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## Ruthenium-catalyzed *ortho*-C-H bond arylation reactions

Christian Bruneau, Rafael Gramage-Doria\* (rafael.gramage-doria@univ-rennes1.fr)

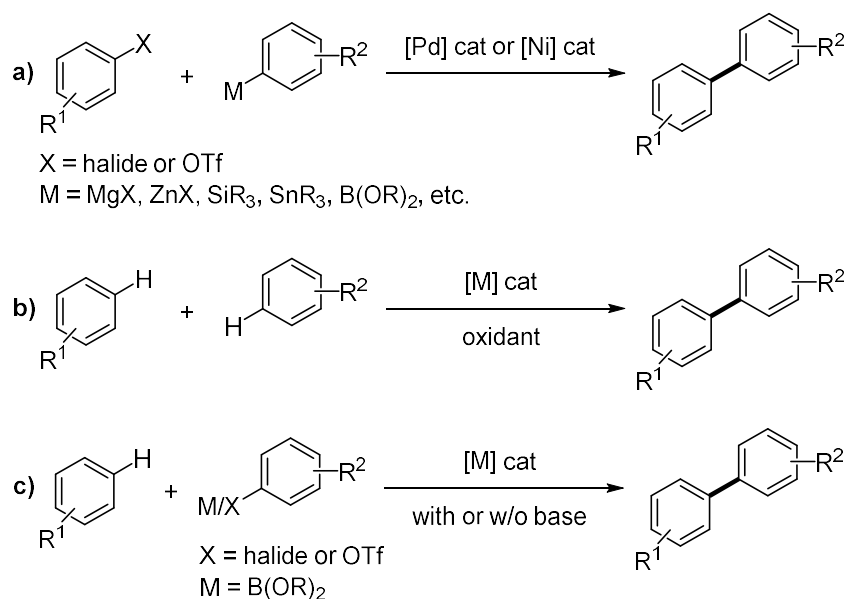
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**Keywords:** ruthenium, C-H bond functionalization, arylation, *ortho*-selectivity, reaction mechanisms

**Abstract:** The highly selective ruthenium-catalyzed *ortho*-C-H bond arylations have met a level of maturity that makes them an attractive tool to achieve unique organic transformations. By means of the manifold mechanisms operating in the presence of different arylating agents and reaction conditions, these methodologies have succeeded in reducing the wastes/steps towards the desired molecules as well as enlarging the chemical space by affording molecules impossible to obtain otherwise. The key achievements in this area are discussed in this chapter.

### 1. Introduction.

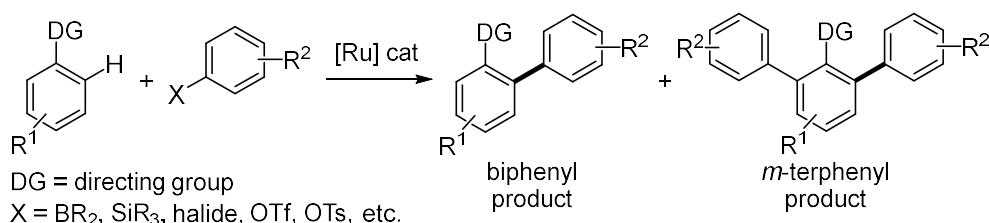
Biaryl and terphenyl cores are widespread structures in many biologically active substances and have useful physical properties in material sciences. The seminal results on the synthesis of biphenyl by connecting two aryl iodide molecules *via* reductive coupling in the presence of copper were reported in 1901 [1] and this concept was further developed [2,3]. Since this discovery, continuous efforts have been devoted to the improvement of these aryl-aryl couplings, mainly based on palladium-catalyzed cross-coupling reactions of aryl (pseudo)halides with organometallic reagents leading to the formation of a new C(sp<sup>2</sup>)-C(sp<sup>2</sup>) bonds (Figure 1a) [4-8].



**Figure 1** Various strategies for the construction of biaryls by metal-catalyzed approaches.

These catalytic methods based on cross-coupling of an aryl halide (or triflate) and an organometallic substrate (B, Sn, Zn, Si, Mg derivative) have brought drastic improvements for the preparation of aryl-aryl bonds but they suffer from some disadvantages. Indeed, the organometallic substrate has to be prepared, which is sometimes not straightforward and the reaction generates metal-containing wastes produced in stoichiometric amounts, which is not compatible with the criteria of sustainable green chemistry in terms of atom economy and environmental aspects (Figure 1a). During the last twenty years, alternative methods involving direct C-H bond activation have emerged. Intermolecular oxidative coupling of two arenes or cross dehydrogenative coupling (CDC) represents a very appealing process since it proceeds *via* activation of two C-H bonds without prefunctionalization, but requires the presence of an oxidant and encounters regio-selectivity issues, which have however been recently tackled by the use of directing groups (Figure 1b) [9-13]. Cross-coupling involving the activation of only one aryl C-H bond has been realized using as cross-coupling partner either an electrophilic aryl (pseudo)halide or an organoboron substrate (Figure 1c). These direct arylation methods have been developed with several transition metal catalysts [14-22] and, typically, involve inexpensive substrates. As such, they are carried out in less steps by reducing waste production compared to the traditional cross-coupling methods. The critical point in these methods is the site-selectivity for the activation of a targeted aromatic C-H bond. This has been solved by the use of directing groups, which temporarily coordinate the metal centre, and orientate the activation of a specific C-H bond. Besides the use of catalysts based on Pd, Rh and Ir, the less

expensive and more affordable Ru-based ones appeared similarly powerful due to similar oxidation states and geometries [23]. In this chapter, we discuss the *ortho*-selective C-H bond arylation of phenyl groups (aryl-aryl bond formation) catalyzed by ruthenium catalysts with the assistance of directing groups (Scheme 1).



**Scheme 1** Ruthenium-catalyzed *ortho*-C-H bond arylation.

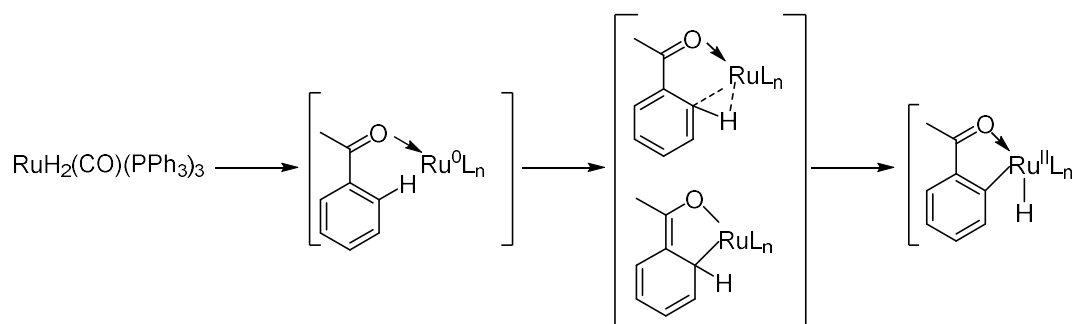
There are many reviews dedicated to directed ruthenium-catalyzed C-C bond formation involving aromatic C-H bond activation/functionalization, most of them include arylation but also alkenylation and alkylation as well as C-heteroatom bond (C-halide, C-N, C-O) formation [24-35]. Arylations proceed *via* various reaction mechanisms and catalytic cycles depending on the nature and especially the oxidation state of the ruthenium catalyst (Ru(0) or Ru(II)). After presenting the different mechanistic aspects of the ruthenium-catalyzed arylation elaborated from experimental and theoretical studies, examples illustrating each type of mechanism are given. We discuss the Ru(0)-catalyzed *ortho*-arylation directed by ketones, and various aspects of the Ru(II)-catalyzed *ortho*-arylation including the nature of the directing groups, arylating agents, site selectivity (mono- and bis-arylation) and show some applications in industry. The directed arylation of five-membered heterocycles such as pyrroles, indoles, furans, thiophenes, and benzofurans are not included in this chapter [36-43].

## 2. Ru-catalyzed *ortho*-C-H bond arylations using low-valent ruthenium pre-catalysts.

### 2.1. Ru-catalyzed *ortho*-C-H bond arylation using low-valent ruthenium pre-catalyst: mechanistic considerations.

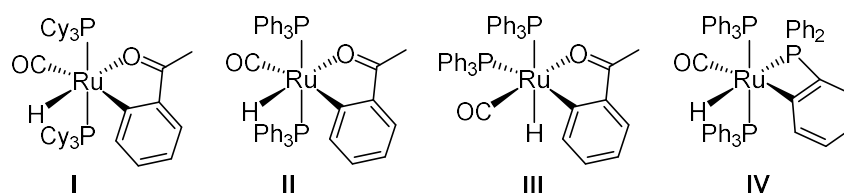
Following the seminal results obtained in the group of Murai on aromatic *ortho*-C-H bond activation/alkylation by a terminal olefin directed by a ketone with  $\text{RuH}_2(\text{CO})(\text{PPh}_3)_3$  or  $\text{Ru}(\text{CO})_2(\text{PPh}_3)_3$  as catalyst precursors [44], this type of ruthenium precursors have found catalytic applications in various directed C-H bond functionalization, in particular in arylation

with aryl boronates. The accepted mechanism is based on the initial coordination of the carbonyl group of the aromatic ketone to the ruthenium(0) center of the active species, either starting from a ruthenium(0) catalyst or generated upon reduction of a ruthenium(II) dihydride complex, bringing the *ortho* C-H bond close to the ruthenium center. By direct interaction of the ruthenium atom with the C-H bond or by 1,4-addition of the ruthenium moiety followed by a 1,2-H shift, a cyclometalated Ru(II) intermediate resulting from a formal oxidative addition could be formed (Scheme 2) [45]. Density functional theory (DFT) studies on activation of *ortho*-C-H bond in aromatic ketones and aldehydes with low valent ruthenium catalysts have confirmed the crucial role of the formation of the ruthenacycle [46]. Further DFT calculations by Lin and Lam [47], and Clot [48], respectively, have shown that the oxidative addition of the *ortho*-sp<sup>2</sup>C-H bond of acetophenone to ruthenium dihydride species required very low energy and was a relatively facile process.



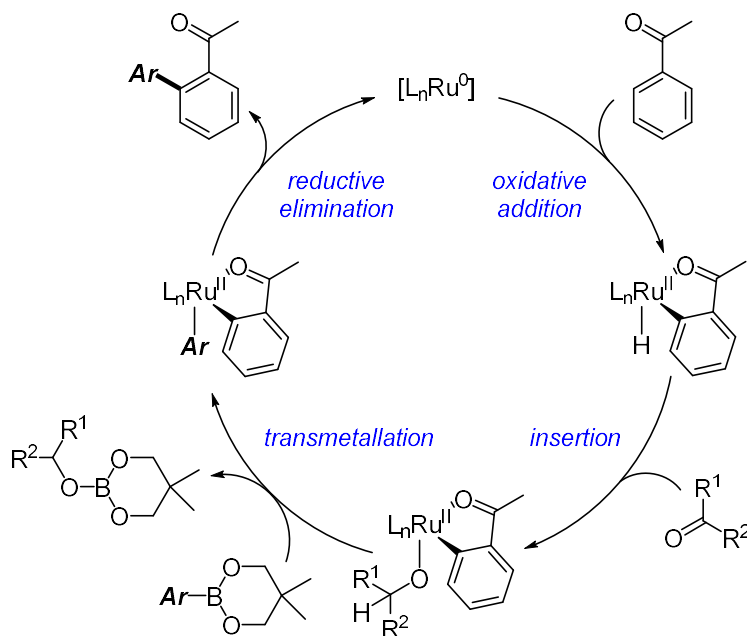
**Scheme 2** Reaction pathway for the *ortho*-C-H bond activation involving oxidative addition at the ruthenium center.

It can be noted that several cyclometalated  $\text{RuH}(o\text{-C}_6\text{H}_4\text{C}(\text{O})\text{Me})(\text{CO})(\text{PR}_3)_2$  complexes ( $\text{R} = \text{Cy}$  (**I**) [49],  $\text{Ph}$  (**II**) [50]) have been isolated and characterized. Among them, those presenting the two phosphine ligands in *trans*-position (**I** and **II**) exhibited poor catalytic activity whereas the *cis*-isomer **III** was identified as a key intermediate in the *ortho*-alkylation of aromatic ketones with olefins (Figure 2) [51]. In addition, it was found that the four-membered ruthenacycle **IV** generated from  $\text{RuH}_2(\text{CO})(\text{PPh}_3)_3$  and resulting from *ortho*-C-H bond activation in a triphenylphosphine ligand was an excellent catalyst for the same reaction.



**Figure 2** *ortho*-Ruthenated complexes relevant for *ortho*-C-H bond arylations.

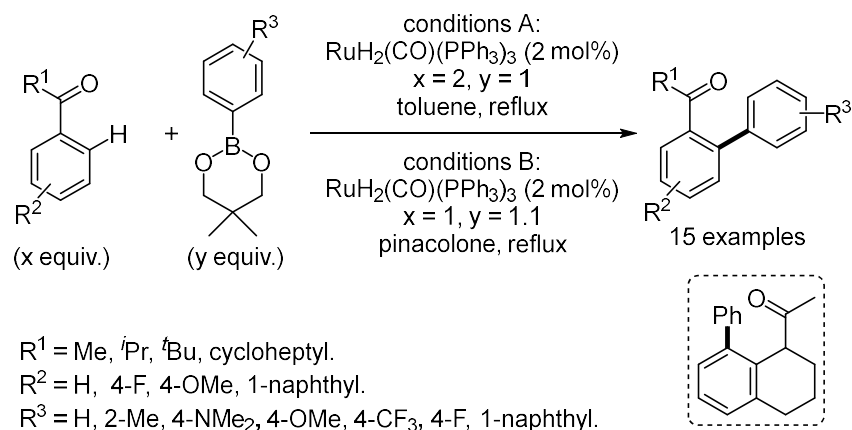
In *ortho*-directed arylation of ketones and imines, this C-H bond activation with ruthenium(0) pre-catalysts has been essentially used with aryl boronate as arylating reagents. In their seminal report, Kakiuchi and co-workers proposed a catalytic cycle where two equivalents of ketone with respect to the arylating agent were necessary to achieve high yield in arylated ketone (Scheme 3) [52]. Indeed, one equivalent of ketone was involved in the formation of an alkoxy ligand by insertion of the carbonyl bond into the ruthenium hydride bond initially generated. Further transmetalation installed the aryl group on the metal center and the final arylated product was obtained by reductive elimination, which concomitantly regenerated a catalytically active ruthenium(0) species. The drawback of this protocol was the loss of one equivalent of valuable aromatic ketone in the overall transformation. In order to circumvent this problem, the use of a reactive sacrificial aliphatic ketone able to produce the alkoxy ligand and act as a scavenger of both the B(OR)<sub>2</sub> moiety and the *ortho*-hydrogen of the ketone substrate made possible the use of equimolar amounts of substrates. The best arylating reagents were aryl boronic acid neopentylglycol esters (Scheme 3), and the most efficient sacrificial ketone was *tert*-butylmethyl ketone (pinacolone) [53]. It must be noted that the catalytic cycle described in Scheme 3 involves Ru(0)/Ru(II) species and that no base/acid is required.



**Scheme 3** General catalytic cycle for the *ortho*-C-H bond arylation of ketones with aryl boronates starting from a Ru(0) pre-catalyst.

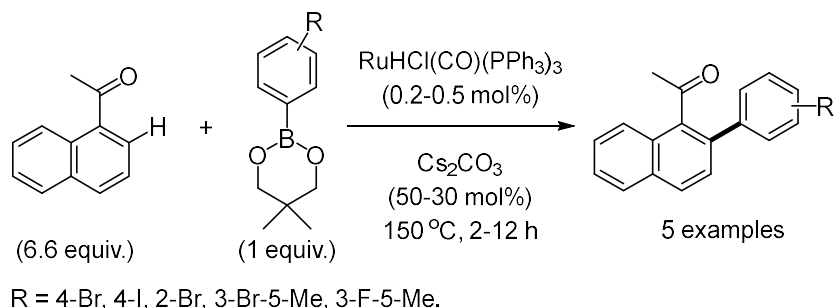
## 2.2. Examples of Ru-catalyzed *ortho*-C-H bond arylations using low-valent ruthenium pre-catalysts.

Ten years after the discovery of the *ortho*-directed C-H bond activation/alkylation of aromatic ketones with olefins in the presence of  $\text{RuH}_2(\text{CO})(\text{PPh}_3)_3$  as precursor of catalytically active  $\text{Ru}(0)$  species [44], the corresponding arylation was shown with arylboronate as source of nucleophilic aryl group [53]. The catalytic cycle for this arylation has been described in Scheme 3 with 5,5-dimethyl-2-phenyl-1,3,2-dioxaborinane, which is the most efficient and used arylating boronate so far. Because, a catalytic cycle consumed 2 equivalents of ketone, the first results were obtained in refluxing toluene with a twofold excess of ketone in order to reach satisfactory yields (conditions A, Scheme 4). The utilization of pinacolone under refluxing conditions (106 °C) both as solvent and sacrificial ketone allowed to work under stoichiometric ratio of substrates with similar efficiencies (conditions B, Scheme 4) [53,54]. With both systems, bis-arylation was observed only with the less sterically hindered ketones, namely acetophenone and phenyl isopropyl ketone, but only monoarylated products were formed from pivalophenone. Electron-donating or withdrawing groups present on the ketone aromatic ring or on the arylating group were well tolerated. It is noteworthy that the directed *ortho*-arylation proceeded also with bicyclic substrates such as 1-acetylnaphthalene,  $\alpha$ -tetralone and benzosuberone. The fact that the reaction also worked with 1-acetyl-1,2,3,4-tetrahydronaphthalene as substrate (framed, Scheme 4) suggests that large six-membered ruthenacycles are at play in the key C-H bond activation step. With acetophenone substrates, the selectivity towards the bis-arylation that was observed even without an excess of arylboronate could be reversed towards mono-arylation by using the  $\text{RuH}_2(\text{CO})(\text{PPh}_3)_3$ /pinacolone system in the presence of a styrene as additive. For instance the reaction of acetophenone (3 equiv.) with 5,5-dimethyl-2-phenyl-1,3,2-dioxaborinane (1 equiv.) provided a mono-/bis-arylation ratio of 15:64 in the absence of styrene, ratio which was reversed to 56:17 in the presence of 1 equivalent of styrene. Mono-arylation products were thus produced in good yields with high selectivity with electron-rich arylboronates [55]. The conversion and selectivity towards mono-arylation of acetophenone was even improved to 70:8 when 2.5 mol% of  $\text{RuHCl}(\text{CO})(\text{P}^i\text{Pr}_3)_2$  containing a trialkylphosphine ligand was used in combination with 5 mol% of CsF and 1 equiv. of styrene [56].



**Scheme 4** Ruthenium-catalyzed *ortho*-C-H bond arylation of aromatic ketones with arylboronates with a low-valent ruthenium pre-catalyst under two different reaction conditions.

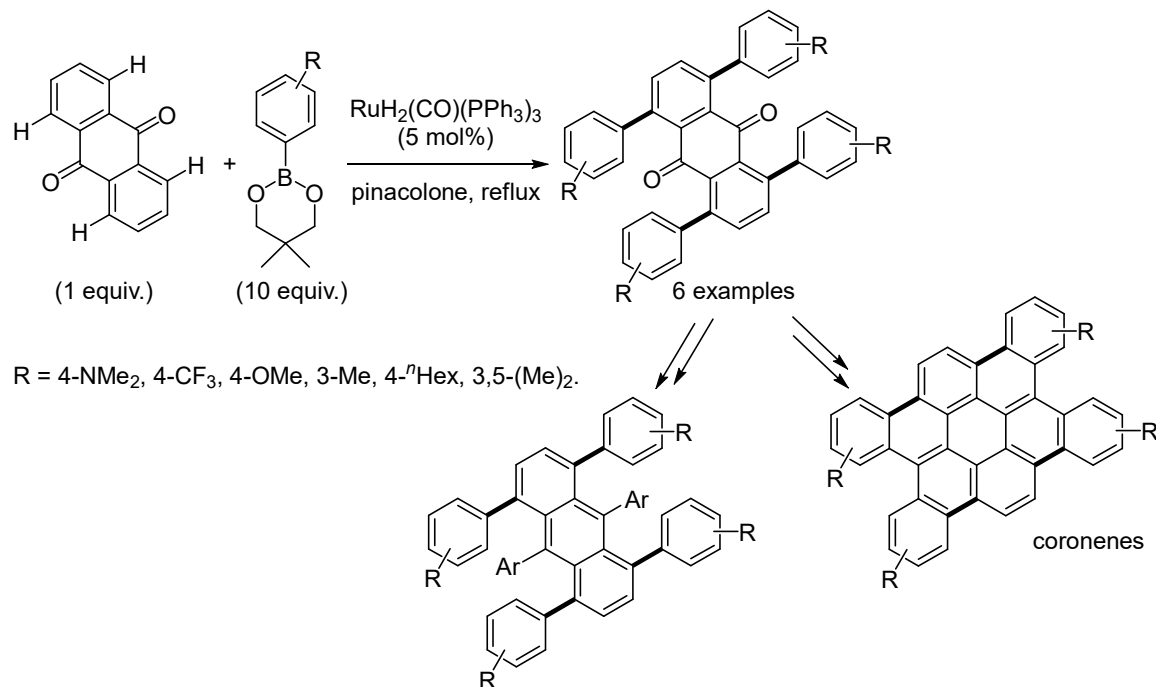
Starting from 1-aclynaphthalene and 2-(4-bromophenyl)-5,5-dimethyl-1,3,2-dioxaborinane, both experimental conditions from Scheme 4 led to very low conversion. In contrast, the presence of a catalytic amount of base ( $\text{Cs}_2\text{CO}_3$ ,  $\text{RbCO}_3$ ,  $\text{CsF}$ ,  $t\text{BuOK}$ ,  $\text{KOH}$ ,  $\text{K}_3\text{PO}_4$ ) promoted the *ortho*-C-H bond arylation up to 83% yield with a very low level (< 5%) of dehalogenation of the bromoaryl group (Scheme 5) [57]. The reactions were carried out at 150 °C with an excess of the ketone without additional solvent. This reactivity of the halogenated arylboronate indicated that, in the presence of the base, the oxidative addition of the aryl bromide to the ruthenium center did not take place significantly and confirmed that the arylboronate was the source of the nucleophilic aryl group. This catalytic system could be applied to various bromo- and iodo-arylboronates but was limited by substitution at the *ortho*-position of the arylboronate. Because arylboronic acids are available for industrial applications, the arylation of 1-aclynaphthalene was successfully carried out with the *in situ* generated halogenated arylboronate at 150 °C in toluene, yielding 78% of the expected brominated *ortho*-arylated product, directly from 4-bromophenylboronic acid and 2,2-dimethylpropane-1,3-diol in the presence of  $\text{RuHCl}(\text{CO})(\text{PPh}_3)_3/\text{Cs}_2\text{CO}_3$ .





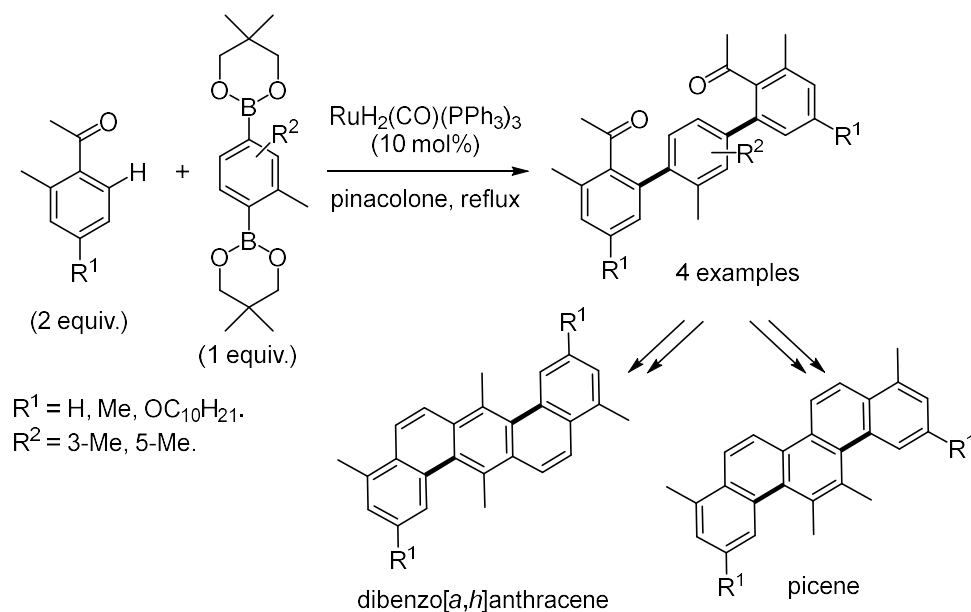
**Scheme 5** Ruthenium-catalyzed *ortho*-C-H bond arylation of 1-acylnaphthalene with halogenated arylboronate partners.

In most cases,  $\text{PPh}_3$  is used as the ligand for the ruthenium pre-catalyst. However,  $\text{RuHCl}(\text{CO})(\text{PAr}_3)_3$  and  $\text{RuH}_2(\text{CO})(\text{PAr}_3)_3$  containing bulky triarylphosphines ( $\text{Ar} = 3\text{-MeC}_6\text{H}_4$ ,  $4\text{-MeC}_6\text{H}_4$ ,  $4\text{-EtC}_6\text{H}_4$ ,  $4\text{-FC}_6\text{H}_4$ ,  $3\text{-MeOC}_6\text{H}_4$ ,  $4\text{-MeOC}_6\text{H}_4$ ,  $3,5\text{-Me}_2\text{C}_6\text{H}_3$ ,  $4\text{-MeO-}3,5\text{-Me}_2\text{C}_6\text{H}_2$ ) also generated efficient catalysts for the arylation with arylboronates.  $\text{RuHCl}(\text{CO})(\text{PAr}_3)_3$  catalysts operated better in acetone/mesitylene mixture at  $140^\circ\text{C}$  with  $\text{CsF}$  as additive and were especially useful for the selective mono-arylation of sterically demanding ketones such as benzophenone. The arylation of the sterically congested 3,5-dimethylphenyl *tert*-butyl ketone was achieved in high yields with  $\text{RuH}_2(\text{CO})(\text{P}(3\text{-MeC}_6\text{H}_4)_3)_3$  [58]. Selective tetra-*ortho*-arylation of anthraquinone has provided an elegant entry to the preparation of polyaromatic structures. The general methodology for the access to hexaarylanthracenes was based on tetra-arylation with an arylboronate followed by arylation of the ketonic groups with an aryl lithium reagent and then reduction of the corresponding alcohol. On the other hand, the synthesis of coronenes involved first *ortho*-directed C-H bond arylation followed by dimethylenation and finally oxidative cyclization promoted by  $\text{FeCl}_3$  (Scheme 6) [59,60].



**Scheme 6** Ruthenium-catalyzed tetra-*ortho*-C-H bond arylation of anthraquinone en route towards polyaromatics.

Under similar conditions, the use of symmetrical diboronates made possible the ring extension in a linear manner starting from acetophenone substrates to give *para*-diarylbenzene products (Scheme 7) [61]. Dibenzo[*a,h*]anthracene and picene derivatives, potential organic field-effect transistor materials, were then produced in two steps after ethylation of the acetyl group and platinum-catalyzed cycloaromatization.

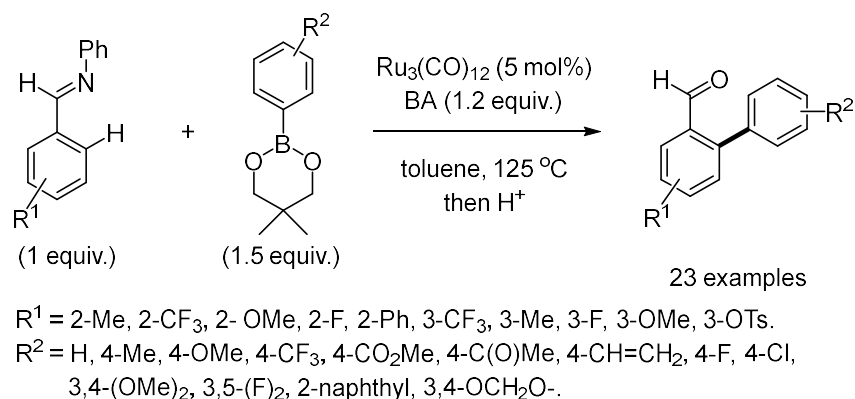


**Scheme 7** Ruthenium-catalyzed *ortho*-C-H bond arylation of acetophenones with arenediboronates.

Catalytic systems based on ruthenium(0) active species have also been used with other directing groups than ketones. In particular the *ortho*-C-H bond arylation of aldimines has been performed in toluene at 125 °C with  $\text{Ru}_3(\text{CO})_{12}$  as Ru(0) pre-catalyst in the presence of benzylideneacetone (BA) as hydride acceptor [62]. The final imines derived from aniline were further hydrolyzed by HCl to recover the *ortho*-arylated aldehydes (Scheme 8). The arylation was tolerant to many functional groups of the arylboronate reagent such as alkyl, alkenyl, vinyl, alkoxy, alkoxycarbonyl, acetyl, halide, trifluoromethyl placed in *meta* and *para* positions. When one *ortho*-position of the aldimine was protected by a methyl, phenyl, trifluoromethyl, methoxy or fluoro group, the second *ortho*-position was efficiently arylated to give the expected *o,o'*-disubstituted aldehyde. Substitution of the aldimine at the *meta*-position of the aryl group by an electron-attracting group (F,  $\text{CF}_3$ ) or a methyl group led to mono-arylation at the less sterically hindered *ortho*-position, whereas bis-arylation took place in the presence of an electron donating group such as MeO or TsO. Similarly, the aldimine arising from benzaldehyde led to bis-arylation in 90% yield. It is also interesting to note that the ketamine

obtained from unsubstituted acetophenone selectively led to the mono-arylation product in 91% yield contrasting with the direct arylation from acetophenone, which gave bis-arylation [53,54].

Rather than moving towards the aldehyde by hydrolysis, profit has been taken from this efficient *ortho*-arylation to include it in a one-pot tandem transformation aiming at the production of sterically hindered aromatic amines. Ruthenium(0)-catalyzed C-H bond arylation was followed by catalytic reduction of the imine in the presence of the catalytically active ruthenium residue either *via* hydrosilylation with Et<sub>3</sub>SiH or *via* hydrogen transfer process with isopropanol [63]. It is noteworthy that in all cases, the aldimine could be generated *in situ* from the aldehyde and the aniline derivative in the presence of MgSO<sub>4</sub> as H<sub>2</sub>O scavenger in the same pot before starting the catalytic sequence.



**Scheme 8** Ruthenium-catalyzed *ortho*-C-H bond arylation of aldimines using a Ru(0) pre-catalyst.

Amides, esters, and nitrile have also been investigated as directing groups for this ruthenium(0)-catalyzed *ortho*-arylation but the results were less conclusive. Amides are not applicable directing groups since in the presence of 4 mol% of RuH<sub>2</sub>(CO)(PPh<sub>3</sub>)<sub>3</sub> at 125-135 °C in toluene for 85 h, only 7% of the *ortho*-phenylated product was obtained from 4-MeOC<sub>6</sub>H<sub>4</sub>CONEt<sub>2</sub> [64]. Aromatic esters have been arylated by 5,5-dimethyl-2-aryl-(1,3,2)dioxaborinanes in the presence of a catalytic amount of RuH<sub>2</sub>(CO)(PPh<sub>3</sub>)<sub>3</sub> (5 mol%) in refluxing pinacolone to form *ortho*-arylated benzoate derivatives. From isopropyl benzoate substrates, both mono- and diarylated esters were formed from 2 equivalents of arylboronate with moderate selectivity towards the diarylated products. From *ortho*-substituted benzoates, moderate yields were obtained and it was noted that the introduction of an electron-withdrawing group such as CF<sub>3</sub> promoted the arylation. Easy hydrolysis under acidic conditions gave access to *ortho*-aryl

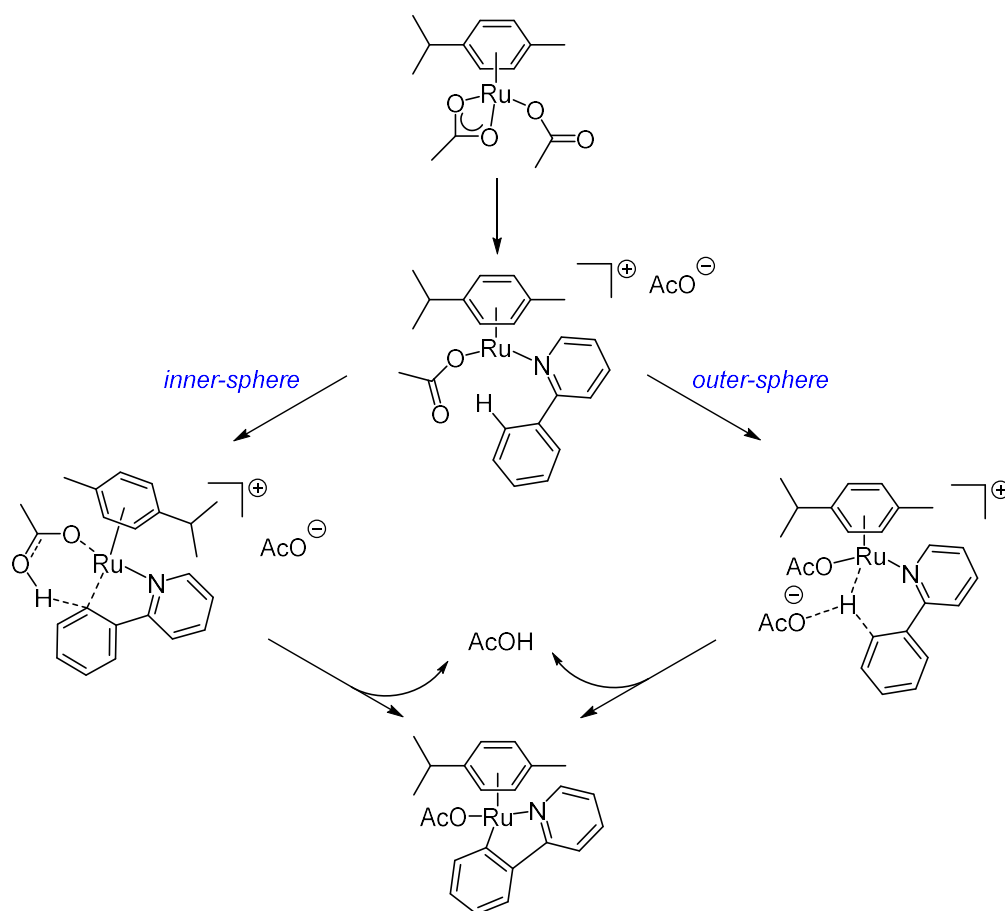
benzoic acids [65]. The nitrile group appeared as a trickier directing group. The best conditions for arylation of aromatic nitriles included the use of  $\text{RuH}_2(\text{CO})(\text{P}(4\text{-MeC}_6\text{H}_4)_3)_3$  in high catalyst loading (10-20 mol%) in pinacolone at 120 °C but also in the presence of  $\text{KHCO}_3$  as a base [66]. Depending on the substitution pattern of the nitrile, mono and di-*ortho*-arylation were observed but also the unexpected arylation at the *para*-position of the nitrile. Finally, it can be mentioned that the same catalytic systems based on ruthenium(0) catalysis are also very efficient under related experimental conditions for *ortho*-arylation of aromatic ketones esters and amides based on C-O and C-N bond cleavage of *ortho*-alkoxy and *ortho*-dialkylamino aromatic substrates [64,67]. In some cases, C-O and C-H bond activation have found complementary applications [60,67c].

### 3. Ru(II)-catalyzed *ortho*-C-H bond arylations with aryl (pseudo)halides.

#### 3.1. Ru(II)-catalyzed *ortho*-C-H bond arylations with aryl (pseudo)halides: mechanistic considerations.

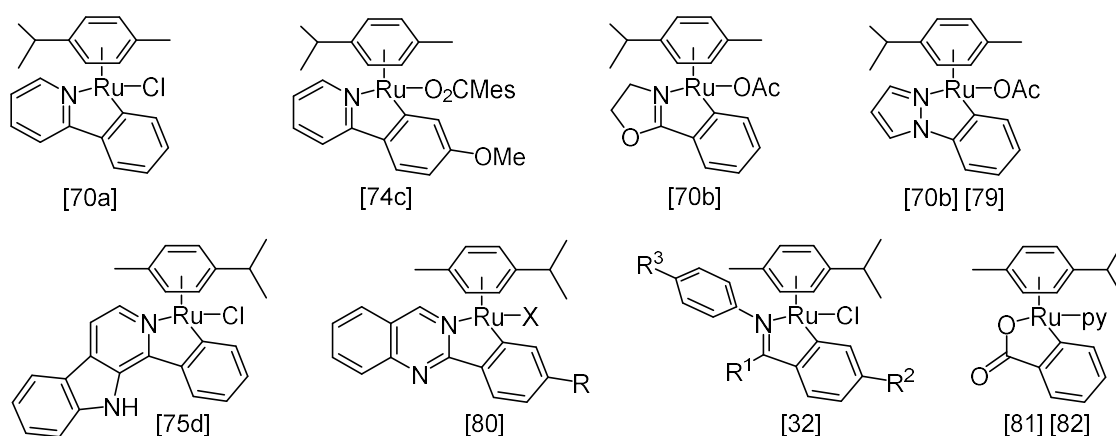
Most of the catalytic processes involving ruthenium(II) catalysts are also based on the initial formation of a five-membered ruthenacycle *via* directed base-assisted C-H bond activation. The most effective directing groups contain a coordinating nitrogen atom that is incorporated in a heteroaromatic ring (pyridine, oxazoline, diazine,azole) or an aliphatic imine. A few examples include a bidentate dinitrogen directing group based on an amino *N*-heterocycle coordinating structure. Some other functional groups such as carboxylic acid, *N*-oxide, acetanilide, thiocarbonyl, featuring an *O*-, *S*- or *P*-coordinating atom have also been evaluated as directing groups. Concerning the key deprotonation event, the presence of a basic ligand such as a carboxylate coordinated to the metal center can induce an inner-sphere concerted metalation-deprotonation (CMD) [68]. The deprotonation can also occur in the presence of an external base *via* an outer-sphere mechanism (external-CMD) [69]. Scheme 9 illustrates these two simplified possibilities from  $\text{Ru}(\text{OAc})_2(p\text{-cymene})$  as catalyst and 2-phenylpyridine as model substrate. It is often difficult to assess the real nature of the interaction since it strongly depends on the experimental conditions [69]. The external deprotonation of 2-phenylpyridine, 2-phenylpyrazole and 2-phenyl-2-oxazoline has been shown experimentally with  $\text{Ru}(\text{OAc})_2(p\text{-cymene})$  as catalyst precursor and in acetonitrile an autocatalytic process where the liberated acetic acid facilitated the coordinated acetate release from the ruthenium centre

was observed [70]. Computational studies have also shown that the deprotonation by an external base was a realistic possibility [71]. It has been demonstrated that mononuclear  $\text{RuCl}_2(p\text{-cymene})(\text{phosphine})$  complexes reacted at room temperature with  $\text{K}_2\text{CO}_3$  in polar solvent to generate  $[\text{Ru}(\eta^2\text{-OCO}_2)(p\text{-cymene})(\text{PR}_3)]$  featuring carbonate as a coordinated base [72]. Inorganic bases such as  $\text{K}_2\text{CO}_3$ ,  $\text{Na}_2\text{CO}_3$ , and  $\text{Cs}_2\text{CO}_3$  have been extensively used in C-H bond functionalization either as sole base [13,73] or associated with a coordinated or free carboxylate [74] and they were considered to act as external base during the C-H bond activation process. In most of the other catalytic systems where ruthenium(carboxylate) complexes were involved either starting directly from a preformed complex  $[\text{Ru}(\text{RCO}_2)_2(p\text{-cymene})]$  or *in situ* generated from  $[\text{RuCl}_2(p\text{-cymene})]_2$  and a carboxylate salt (or carbonate + carboxylic acid - essentially  $\text{AcOH}$ ,  $\text{PivOH}$ ,  $\text{MesCO}_2\text{H}$ ), an inner-sphere mechanism has been proposed [75]. The same type of inner-sphere deprotonation was envisioned when the coordinated base was a secondary phosphine oxide [76] or a carbonate [77]. Some calculations have shown that the energies of the outer- and inner-sphere mechanisms were very close and it was difficult to ascribe the dominant mechanism [78].



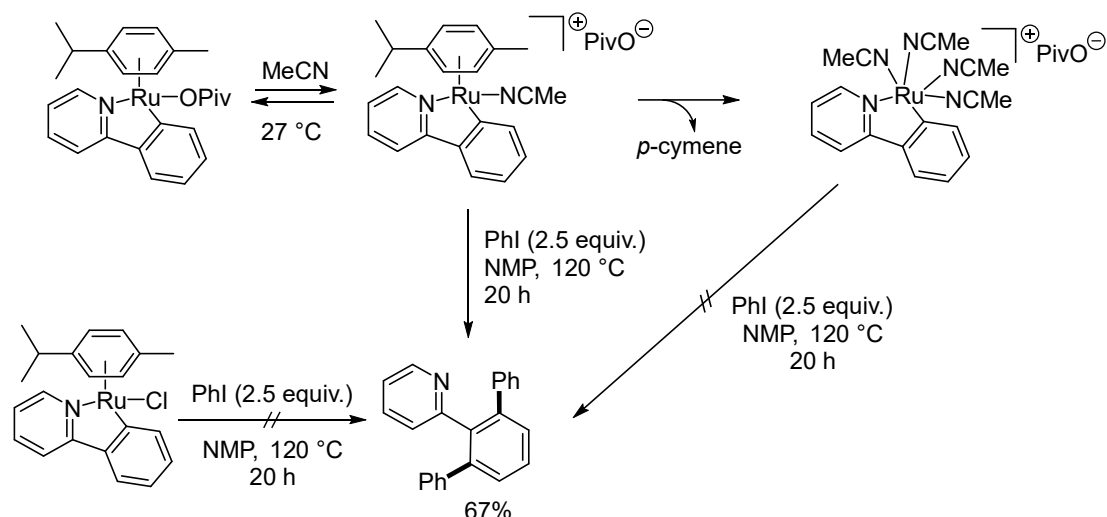
**Scheme 9** Proposed transition states for the ruthenium-mediated *ortho*-C-H activation based on internal and external carboxylate deprotonation.

Whereas ruthenium complexes bearing an *ortho*-metalated chelate resulting from oxidative addition of a C-H bond to a Ru(0) center are scarce, there are many metalacyclic ruthenium complexes resulting from deprotonation processes with Ru(II) precursors reported in the literature in the context of *ortho*-directed C-H bond arylation. In Figure 3 are gathered some examples with various directing groups including pyridine, oxazoline, pyrazole, imine, and carboxylate [79-82].

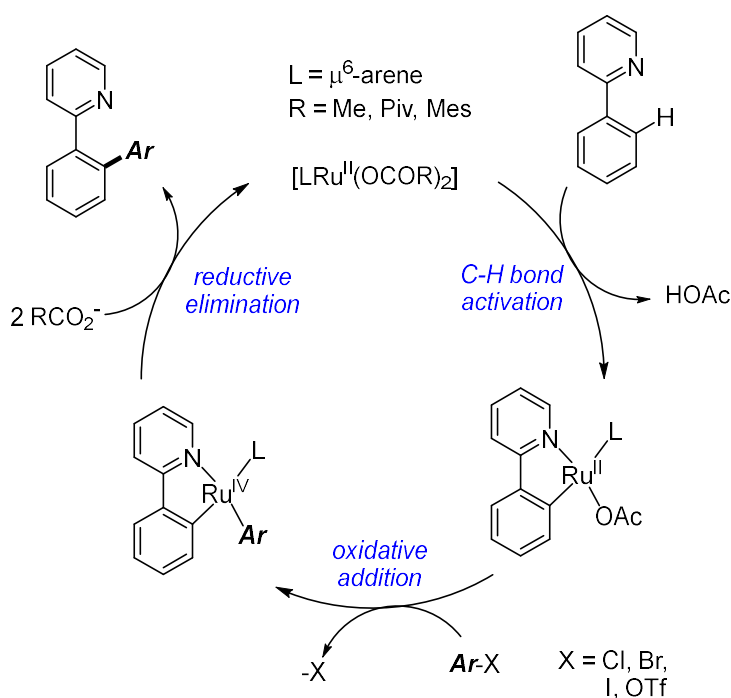


**Figure 3** Selected examples of isolated and characterized *ortho*-C-H bond cyclometalated ruthenium(II) complexes with their associated references in brackets.

The next step of the catalytic cycle corresponds to the oxidative addition of the aryl (pseudo)halide to the ruthenium center leading to the formation of a Ru(IV) intermediate. It was shown by Jutand that at room temperature in a polar coordinating solvent such as acetonitrile, the carboxylate ligand from  $[\text{Ru}(\text{OAc})_2(p\text{-cymene})(o\text{-C}_6\text{H}_4\text{-pyridine})]$  complex was reversibly released to generate a cationic species, which further lost the *p*-cymene ligand (Scheme 10) [70]. The reaction with an excess of phenyl iodide to form the *ortho,ortho'*-diarylated phenylpyridine took place only with a cationic *ortho*-metalated ruthenium species still featuring a *p*-cymene ligand, whereas the cationic ruthenium moieties with no arene ligand and the neutral *ortho*-metalated  $[\text{RuCl}(p\text{-cymene})(o\text{-C}_6\text{H}_4\text{-pyridine})]$  complex with a non-labile chloride ligand were inactive under these conditions. Accordingly, a simplified reaction mechanism is believed to take place *via* C-H activation on the substrate, oxidative addition with aryl (pseudo)halides and reductive elimination towards product formation as key elementary steps (Scheme 11).



**Scheme 10** Reactivity of relevant intermediates in ruthenium-mediated *ortho*-C-H bond arylation starting from  $[\text{RuCl}_2(p\text{-cymene})]_2$  precursor.



**Scheme 11** General and simplified catalytic cycle for the *ortho*-C-H bond arylation with aryl (pseudo)halides starting from a Ru(II) pre-catalyst.

Stoichiometric investigations of the reactivity of *ortho*-metalated  $[\text{RuX}(2\text{-}(p\text{-tolyl})\text{quinazolino})(p\text{-cymene})]$  ( $\text{X} = \text{Cl, Br}$ ) complexes with aryl halides have confirmed the necessity of generating cationic species as no reactivity was observed in the absence of carboxylate. It was also proposed that the *p*-cymene ligand was released and formally replaced by the aryl halide as ligand before oxidative addition [80]. The

dehydrogenative coupling of the substrate bearing the directing group has also been observed as a competing and sometimes major reaction during C-H bond functionalization, showing that the *p*-cymene ligand of the ruthenium catalyst precursor was released before oxidative addition of the aryl halide (see section 3.3) [83-84]. The selectivity towards dehydrogenative coupling or arylation was shown to be controlled by stereoelectronic properties of both reagents and the release of the *p*-cymene ligand was observed experimentally (see section 3.3) [85].

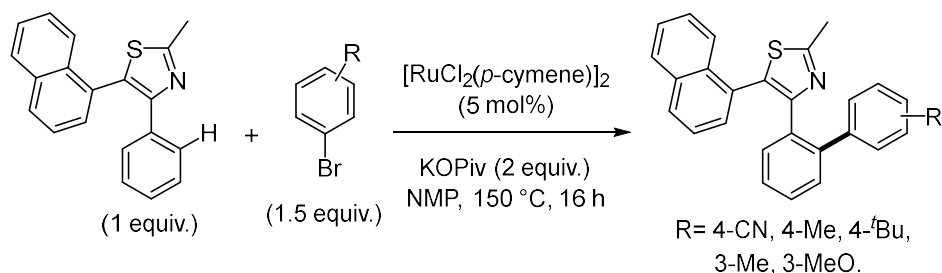
### 3.2. Examples of *ortho*-C-H bond arylations with aryl (pseudo)halides with arene-containing ruthenium(II) pre-catalysts.

When the substrate possessed only one available *ortho*-position, the main focus of the studies have been devoted to investigation of functional group tolerance and improvement of the efficiency of catalytic systems to reach high conversion [86-91]. When two *ortho*-positions were available for direct functionalization, it has been shown that working with an excess of arylating reagent in most cases favored the bis-arylation process. Another recurrent observation is that when the nucleophile bears a *meta*-substituent on the aromatic ring, an *ortho*-C-H bond mono-arylation takes place at the *para*-position of this substituent, due to steric constraint at the other *ortho*-position. However, some parameters inherent to the nature of the directing group and the arylating reagent as well as the catalytic system were found to be crucial to favor mono-arylation processes.

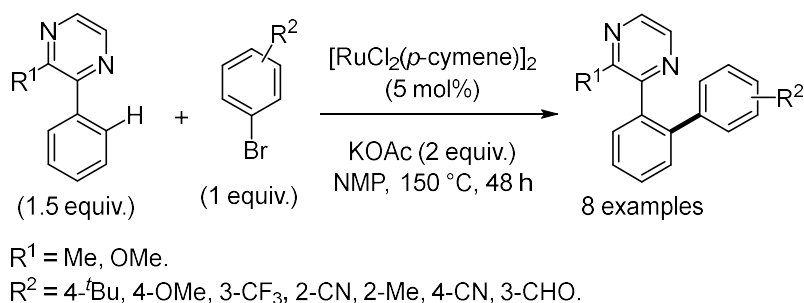
In the presence of a strongly coordinating directing group, typically an aromatic *N*-heteroaryl group (2-pyridyl, 2-oxazolyl, imidazolyl, pyrazolyl, tri- and tetrazolyl) or an imine, the formation of diarylated products is highly favored and can be driven to completion in the presence of an excess of arylating reagent [71a,76b,92-97]. However, this general trend can be reversed when the directing group presents some steric hindrance in the neighborhood of the *ortho*-position of the phenyl group. For instance, the presence of an aryl group in 2-methyl-4-phenyl-5-arylthiazoles promoted the *ortho*-directed mono-arylation of the phenyl group without any formation of the diarylated product (Scheme 12), due to the steric influence of an  $\alpha$ -naphthyl group [98a]. Similarly, only mono-arylation took place when the directing group was a 3-substituted 1,4-pyrazin-2-yl (Scheme 13) [98b] or a imido[1,5-*a*]azine [98c] or a 3,5-dimethylpyrazole [98d] amongst others [98e,98f]. The sterically demanding *N*-benzyltetrazole reacted with methyl *para*-chlorobenzoate to give 77% of monoarylated product with less than 10% of bis-arylation (Scheme 14) [75c]. In this catalytic system, the coordinated *N*-protected



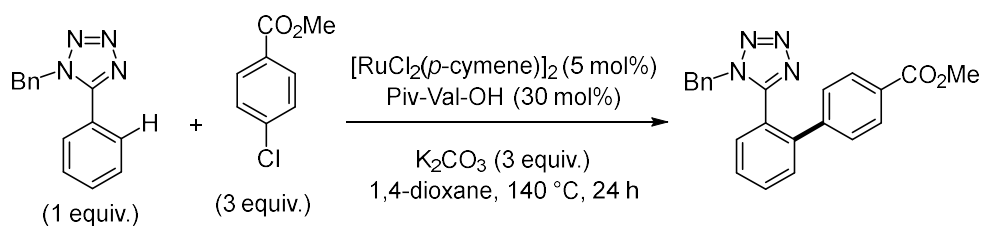
amino acid Piv-Val-OH contributed to the selectivity and also to the productivity of this catalytic arylation as compared to other carboxylic acids.



**Scheme 12** Ruthenium-catalyzed *ortho*-C-H bond mono-arylation using aryl bromides and thiazole as the directing group.

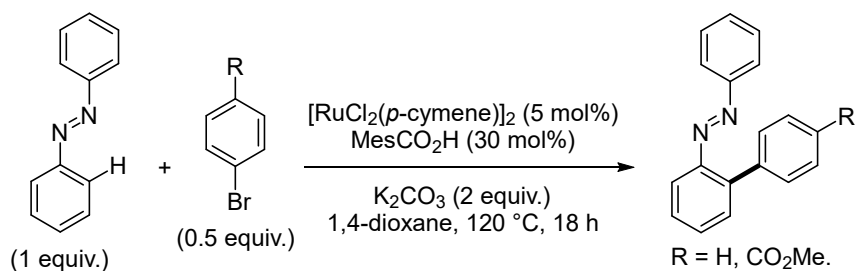


**Scheme 13** Ruthenium-catalyzed *ortho*-C-H bond mono-arylation using aryl bromides and pyrazine as the directing group.



**Scheme 14** Ruthenium-catalyzed *ortho*-C-H bond mono-arylation using an aryl chloride and tetrazole as the directing group.

In the presence of weak coordinating directing groups, the formation of mono-arylated products is usually favored. This family of directing groups includes amido, diazo and carboxylic acid functional groups. From azoarenes containing four potentially functionalizable *ortho*-positions, the selective mono-arylation was reported with substoichiometric amounts of aryl bromide in the presence of a ruthenium carboxylate catalyst (Scheme 15) [75b].



**Scheme 15** Ruthenium-catalyzed *ortho*-C-H bond mono-arylation of azoarenes using aryl bromides.

As soon as it was discovered, the pioneers of direct C-C bond formation involving ruthenium-catalyzed C-H bond activation pointed out the role of phosphine in the site-selectivity of arylation of aromatic substrates featuring a strong coordinating directing group. In Table 1 are gathered examples related to mono-arylation of 2-phenylpyridine. The general trend is that the presence of the phosphine coordinated to the ruthenium center slows down the rate of the second arylation leading to monoarylated products when equimolar amounts of substrates are used. In many cases, the presence of a simple triarylphosphine [99,102,103] provide this selectivity and more bulky phosphine have also been used for this purpose [100,101,104].

**Table 1.** Influence of phosphane ligands in the ruthenium-catalyzed *ortho*-C-H bond arylation of 2-phenylpyridine with aryl (pseudo)halides.

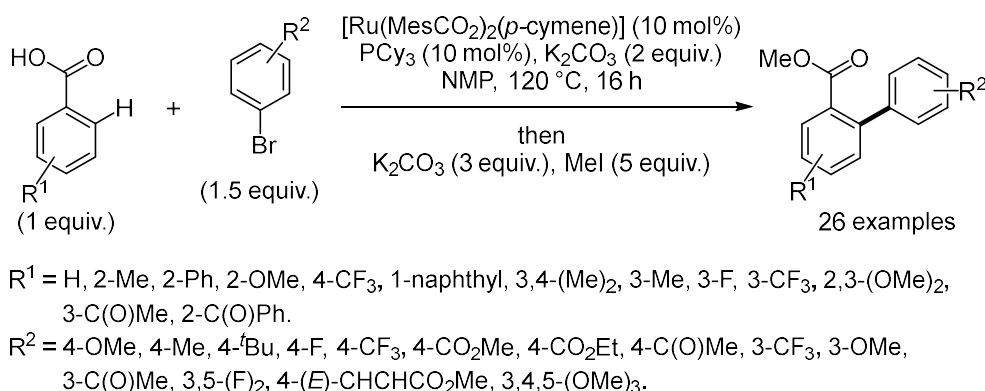
R	X	<i>x</i>	[Ru] cat.	PR <sub>3</sub>	Solvent	Conv. (%)	mono:bis ratio	Ref.
H	Br	1	[Ru1]	PPh <sub>3</sub>	NMP	82	71:11	[99]
H	OTf	1	[Ru1]	PPh <sub>3</sub>	NMP	68	61:7	[99]
H	Cl	1	[Ru1]		NMP	96	96:4	[100]
H	Cl	1	[Ru2]		NMP	R= H, 85 R= Ph, 78	76:9 70:8	[101]
H	Cl	0.8	[Ru2]	PPh <sub>3</sub>	H <sub>2</sub> O	92	95:5	[102]
OMe	Br	0.8	[Ru1]	P( <i>p</i> -Tol) <sub>3</sub>	Bu <sub>4</sub> NOAc	76	64:12	[103]
OMe	Cl	2.2	[Ru1]		NMP	94	81:13	[104]

[Ru1] = [RuCl<sub>2</sub>(arene)]<sub>2</sub> (arene = benzene or *p*-cymene).

[Ru2] = RuCl<sub>2</sub>(*p*-cymene)(PR<sub>3</sub>).

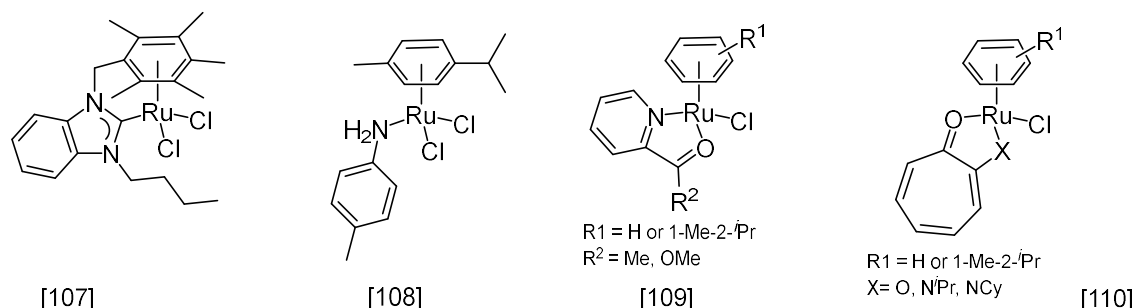
Tricyclohexylphosphine (PCy<sub>3</sub>) combined with [Ru(O<sub>2</sub>CMes)<sub>2</sub>(*p*-cymene)] complex is also an excellent ligand to generate an active and selective catalytic system for the mono-arylation of benzoic acid derivatives involving weak O-Ru interaction (Scheme 16) [81a,81c]. A similar catalytic behavior was encountered replacing PCy<sub>3</sub> for PEt<sub>3</sub>·HBF<sub>4</sub> [82a]. The influence of

phosphane ligands for ruthenium-catalyzed *ortho*-C-H bond arylation using 8-aminoquinoline as the directing group has been studied as well [82c,82d].



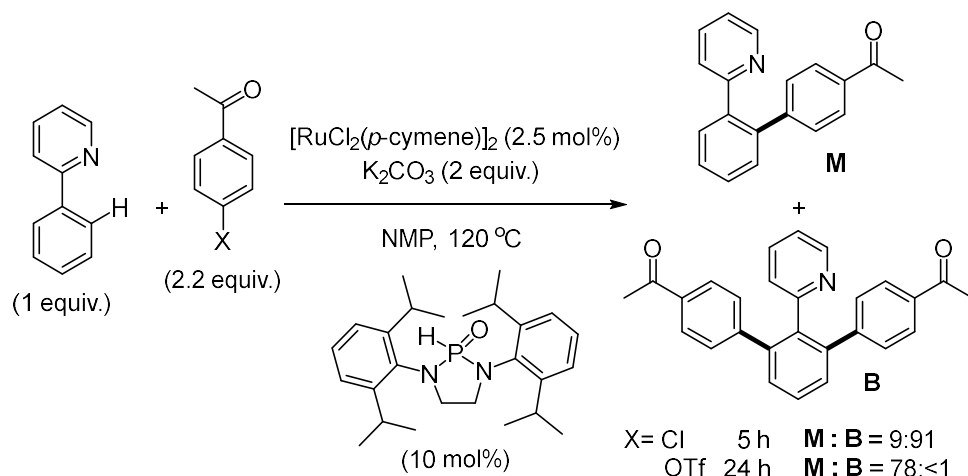
**Scheme 16** Ruthenium-catalyzed *ortho*-C-H bond mono-arylation of benzoic acid derivatives using aryl bromides.

Whereas the bis-arylation of ketimines has been successfully achieved with a catalytic system based on  $[\text{RuCl}_2(p\text{-cymene})]$  and potassium carbonate as a base [93], selective mono-arylation was obtained when  $\text{PPh}_3$  [105] or the sterically demanding  $(\text{adamantyl})_2\text{P(O)H}$  phosphine oxide were added as ligand [106]. Besides phosphine-containing ruthenium(II) complexes, other (arene)ruthenium(II) complexes containing monodentate ligands such as aniline or bidentate ligands such as those represented in Figure 4 displayed high selectivity for mono-arylation of 2-phenylpyridine by aryl chlorides in water in the presence of  $\text{K}_2\text{CO}_3$  as a base [107-110]. The mono- vs bis-arylation can also be controlled in water media by the use of ruthenium(II) complexes containing ferrocenylphosphino sulfonate ligands with different stereoelectronic substitution patterns [111a], using acetamide as co-catalyst [111b] or under microwave conditions [111c,111d], respectively.

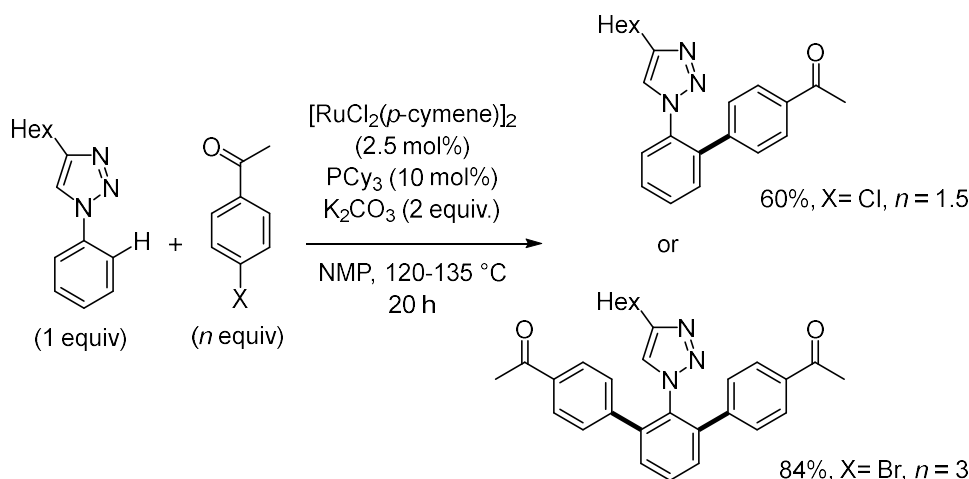


**Figure 4** Selected ruthenium(II) catalyst enabling *ortho*-C-H bond mono-arylation of 2-phenylpyridine derivatives with aryl (pseudo)halides, with their associated references in brackets.

Additionally, it is worth mentioning that whatever the other criteria favorable to mono- or bis-arylation, the nature of the leaving group of the arylating reagent may have some influence not only on reactivity but also on site-selectivity towards mono- or bis-arylation. This is illustrated in the two examples described in Scheme 17. The *ortho*-arylation of 2-phenylpyridine with a ruthenium(II) precursor combined with a sterically hindered diaminophosphine oxide provided the monoarylated product with an aryl tosylate as electrophile source whereas the aryl chloride gave the bis-arylated product selectively even at lower temperature with shorter reaction time (Scheme 17) [88]. Similarly, with the same catalytic system, the aryl bromide as electrophile led to the sole formation of the bis-arylated product. On the other hand, the aryl chloride gave the mono-arylated product (Scheme 18) [89]. The mono- vs bis-arylation was also explored by utilizing biologically-relevant 6-phenylpurine and 6-arylpurine nucleosides as substrates and aryl iodides as arylating agents [112]. Besides aryl (pseudo)halides, phenols [113] and diaryliodonium salts [114] were found as suitable arylating agents, the formers provided they were *in situ* transformed in tosylate derivatives in water media [113].

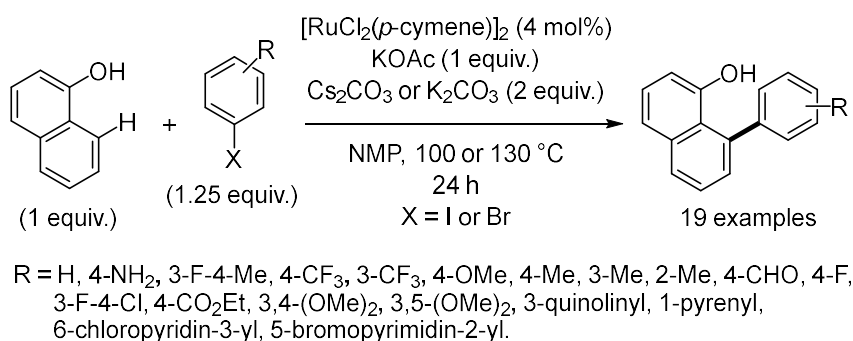


**Scheme 17** Influence of the leaving group (Cl vs OTf) on the arylating reagent for the mono- vs bis-arylation in ruthenium-catalyzed *ortho*-C-H bond arylation.



**Scheme 18** Influence of the leaving group (Cl vs Br) on the arylation ratio for the mono- vs bis-arylation in ruthenium-catalyzed *ortho*-C-H bond arylation.

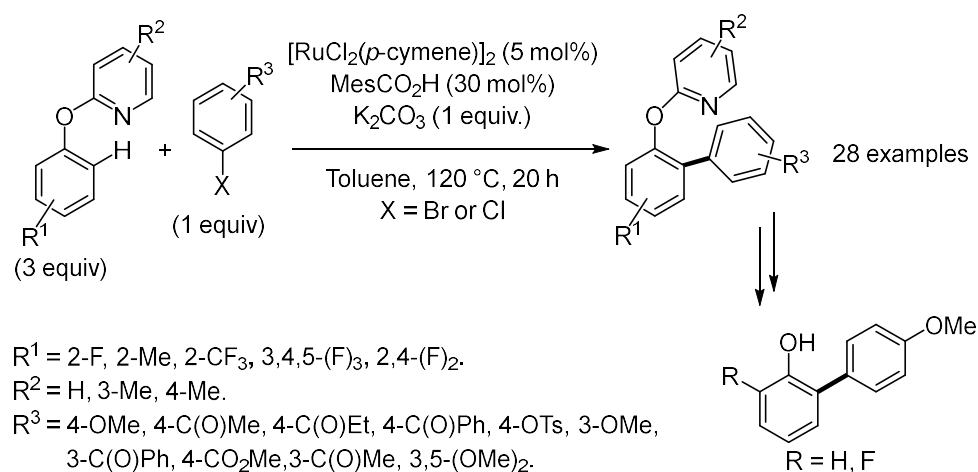
A rare case of hydroxyl-directed ruthenium-catalyzed *ortho*-C-H bond arylation has been reported by using 1-naphthols as substrates and aryl halides under phosphane-free conditions [115]. It gives access to non-trivial, mono-arylated 8-aryl-1-naphthols *via* peri-C-H activation (Scheme 19). Whereas electron-poor aryl iodides reacted smoothly at 100 °C, a higher reaction temperature of 130 °C was required for electron-rich or sterically-demanding aryl iodides as well as aryl bromides that need higher energy for oxidative addition when compared to aryl iodides. Importantly, this methodology broadens the functional group tolerance reported under palladium catalysis [116].



**Scheme 19** Ruthenium-catalyzed *ortho*-C-H bond arylation of 1-naphthol with (hetero)aryl iodides and bromides.

All the above-discussed ruthenium-catalyzed *ortho*-C-H bond arylations involve the formation of five-membered ruthenacycle intermediates. Interestingly, there are also examples of ruthenium-catalyzed *ortho*-C-H bond arylations with substrates leading to formation of larger six-membered ruthenacycles. For instance, 2-phenoxy pyridine derivatives underwent selective

*ortho*-C-H bond arylation at the phenoxy site upon reaction with aryl bromides or aryl chlorides under ruthenium/carboxylate catalysis (Scheme 20) [117]. After a two-step removal of the directing group, *ortho*-arylated phenols were obtained (Scheme 20). A similar ruthenium-based methodology was applied to the late-stage *ortho*-C-H bond arylation of *N*-methylated diflufenican which contains a phenoxy pyridine core [118]. In the same context, ruthenium-catalyzed *ortho*-C-H bond (hetero)arylations were achieved with 2-benzoylpyridine derivatives [119] as well as with (2-biphenyl)diarylphosphines and (2-biphenyl)dialkylphosphines *via* six-membered cycloruthenated intermediates [120].

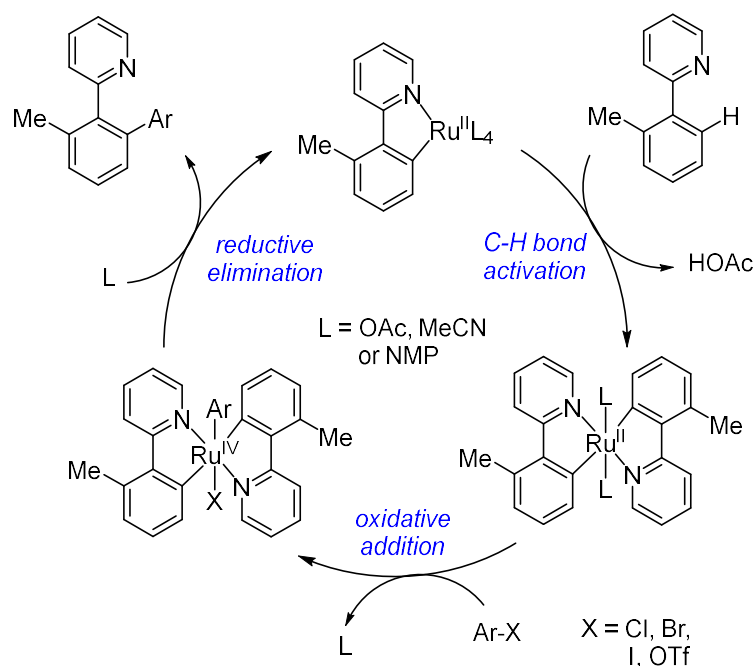


**Scheme 20** Ruthenium-catalyzed *ortho*-C-H bond arylation of 2-phenoxy pyridine derivatives with aryl iodides and chlorides en route to 2-arylated phenols.

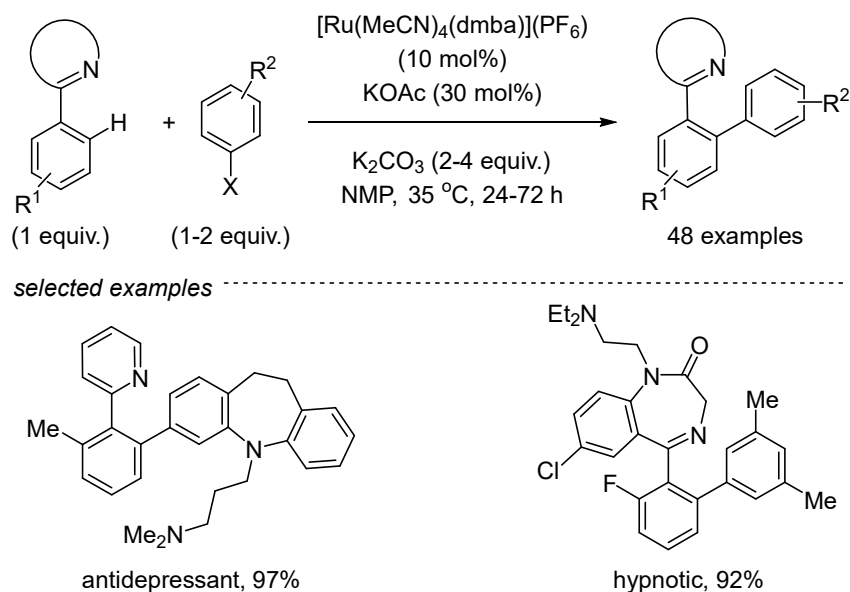
### 3.3. Bis-cycloruthenated species as key intermediates in *ortho*-C-H bond arylations.

In 2018, Larrosa and co-workers demonstrated by kinetic studies that the *p*-cymene ligand attached to the  $[\text{RuCl}_2(\textit{p}\text{-cymene})]_2$  pre-catalyst species displayed an inhibitory effect in the *ortho*-C-H bond arylations using aryl (pseudo)halides as coupling partners [121]. As a result, high temperatures are typically required which are sometimes incompatible with sensitive functional groups. Thanks to NMR spectroscopy studies, further supported by X-ray diffraction studies, the formation of *p*-cymene-free, bis-cycloruthenated species involving *ortho*-C-H bond activation of two substrates at the same ruthenium center was unambiguously identified (Scheme 21). The formation of such species precedes the oxidative addition with aryl (pseudo)halides and the catalytic cycle closes with reductive elimination (Scheme 21). Such reaction mechanism is responsible for making possible ruthenium-catalyzed *ortho*-C-H bond arylations at a mild reaction temperature of 35 °C. To avoid the detrimental formation of

catalytic quantities of undesired arylation at the catalyst, Larrosa and co-workers found that  $[\text{Ru}(\text{dmba})(\text{MeCN})_4](\text{PF}_6)$  complex ( $\text{dmba} = N,N$ -dimethylbenzylamine) behaved as a superior pre-catalyst preventing catalyst degradation and offering a broad substrate compatibility including many substrates relevant for medicinal chemistry (Scheme 22). Note that DFT calculations unraveled that *p*-cymene-free ruthenium intermediate species were energetically more accessible than the *p*-cymene-ligated ones in *ortho*-C-H bond arylations [122].



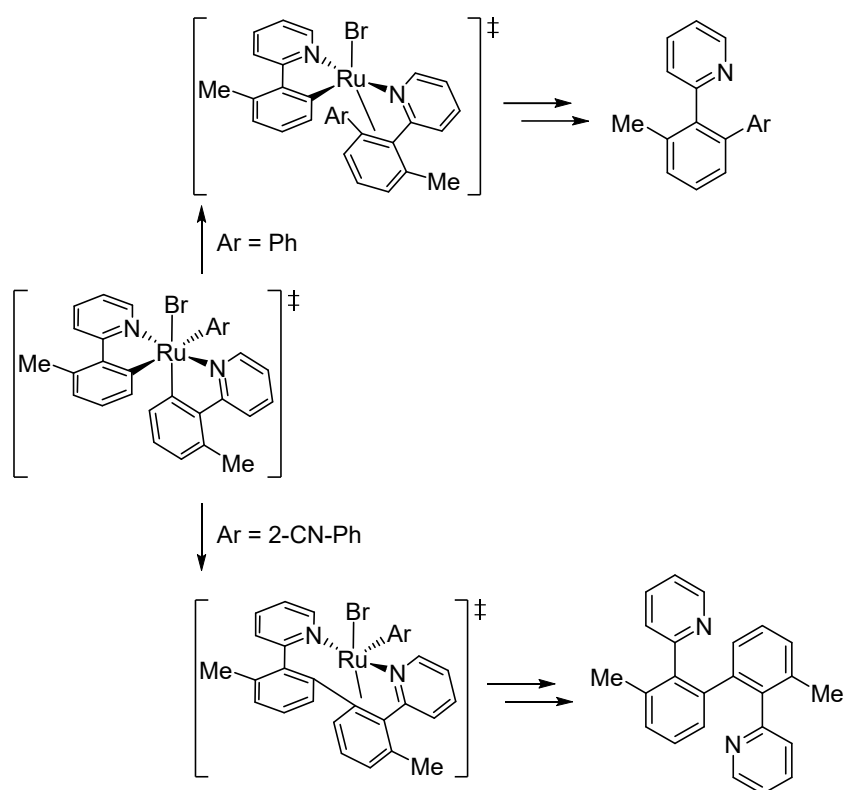
**Scheme 21** Larrosa's reaction mechanism for the *ortho*-C-H bond arylation *via* Ru(II/IV) manifold involving bis-cycloruthenated species prior to oxidative addition.





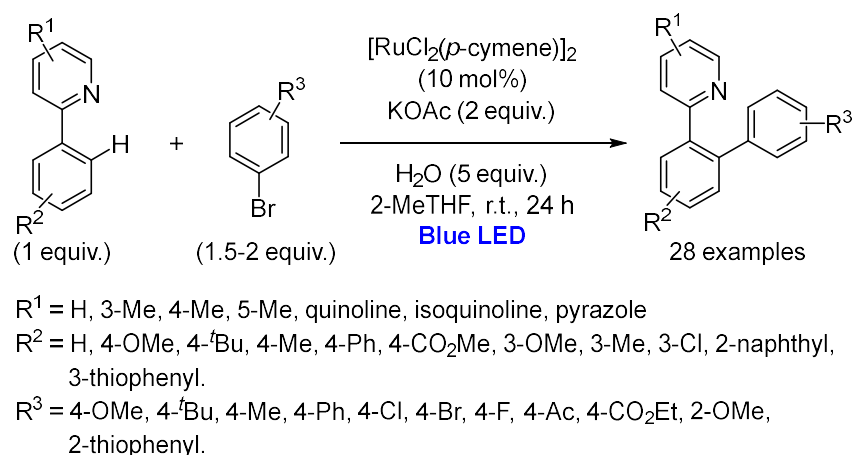
**Scheme 22** General and mild ruthenium-catalyzed *ortho*-C-H bond arylation with aryl (pseudo)halides towards late-stage functionalization of pharmaceuticals.

Ackermann and co-workers later demonstrated that a similar reaction mechanism operates using  $[\text{RuCl}_2(p\text{-cymene})]_2$  as the pre-catalyst at higher temperatures of 120 °C [84]. A combination of experimental studies and DFT calculations suggested that *p*-cymene-free bis-cycloruthenated species are key intermediates upon oxidative addition with aryl halides (Scheme 23). Noteworthy, the C-H bond cleavage event is in line with a base-assisted internal electrophilic substitution (BIES) instead of a concerted metalation/deprotonation (CMD) pathway. The formation of key octahedral ruthenium(IV) species appear to be the turnover-limiting step and the nature of the aryl ligand controls whether *ortho*-C-H bond arylation or oxidative homo-coupling occur. In the former case the aryl moiety acts as an electron-withdrawing spectator ligand (Scheme 23). This behavior is strongly highlighted using aryl halides with electron-withdrawing substituents in the 2-position, such as 2-CN, and with iodides rather than bromides.

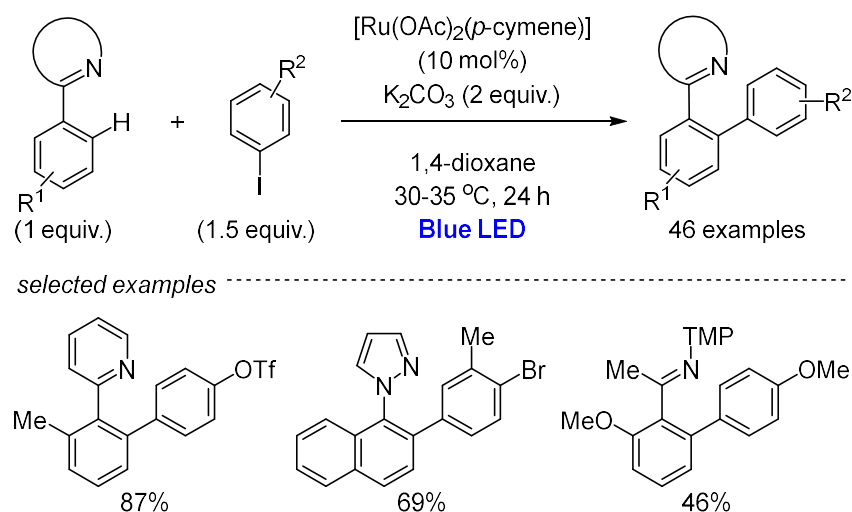


**Scheme 23** A common ruthenium(IV) intermediate leads to direct *ortho*-C-H bond arylation (top) or oxidative homo-coupling (bottom) depending on the stereoelectronic nature of the aryl ligand.

The groups of Greaney and Ackermann, independently, showed that bis-cycloruthenated species prior to oxidative addition also form under catalytic conditions starting from  $[\text{RuCl}_2(p\text{-cymene})]_2$  pre-catalyst complex under photo-irradiation (blue LED) [123,85]. Importantly, the ruthenium-catalyzed *ortho*-C-H bond arylations were conducted at mild reaction temperature (r.t. to 35 °C) thanks to the dissociation of the *p*-cymene ligand from the ruthenium pre-catalyst for further engaging in a catalytic cycle similar to that reported by Larrosa (*vide supra*) [121]. The reaction conditions required high catalytic loadings of ruthenium (20 mol%), which is twice the loading reported by Larrosa's work [121]. Greaney's conditions also needed the use of  $\text{H}_2\text{O}$  in 2-MeTHF as the solvent and were better suited for aryl bromides (Scheme 24) [123]. On the other hand, Ackermann's conditions comprised  $\text{K}_2\text{CO}_3$  in 1,4-dioxane as the solvent and proved selective for aryl iodides, leaving unreactive otherwise sensitive functional groups such as bromides and triflates, which is a relevant finding for synthetic purposes (Scheme 25) [85].

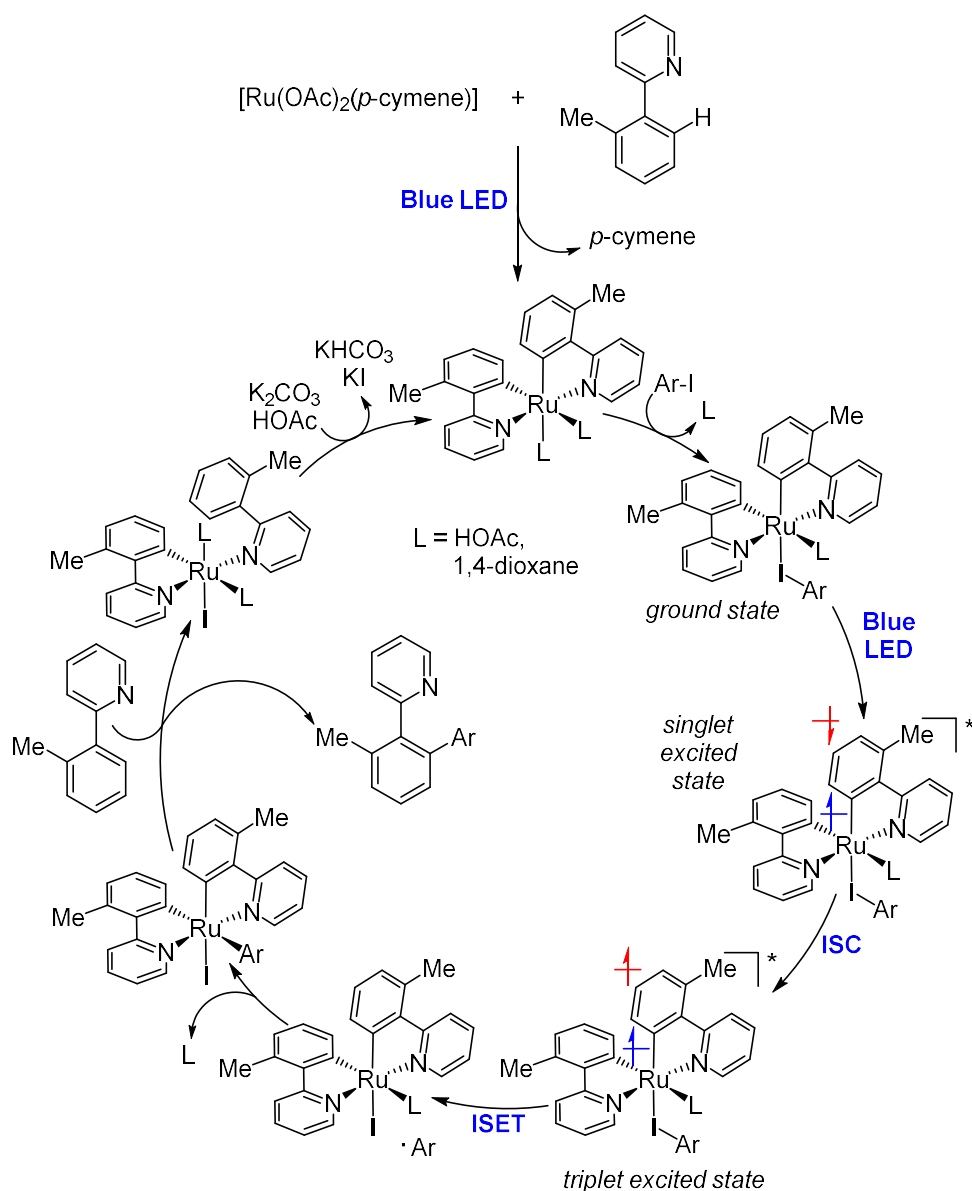


**Scheme 24** Ruthenium-catalyzed *ortho*-C-H bond arylation with aryl bromides under visible light irradiation at room temperature.



**Scheme 25** Ruthenium-catalyzed *ortho*-C-H bond arylation with aryl iodides under visible light irradiation at ambient temperature. TMP = 3,4,5-trimethoxyphenyl.

Ackermann's group reported on DFT calculations of the ruthenium-catalyzed *ortho*-C-H bond arylation with aryl iodides under visible light irradiation at room temperature [85]. The ruthenium(II/IV/II) manifold mechanism involves a first initial formation of bis-cycloruthenated species with the substrate facilitated by photo-induced *p*-cymene decoordination (Scheme 26). Ligand exchange with the aryl iodide coupling partner leads to a iodo-coordinated bis-cycloruthenated species that undergo blue-light-absorption excitation to form the corresponding singlet excited state species. Further relaxation *via* intersystem crossing (ISC) forms a long-lived triplet ruthenium species that undergoes an inner-sphere electron transfer (ISET) generating a phenyl radical that recombines at ruthenium. Further reductive elimination affords the *ortho*-C-H bond arylated product with concomitant coordination of a new substrate that undergoes carboxylate-assisted cycloruthenation and continues the catalytic cycle.

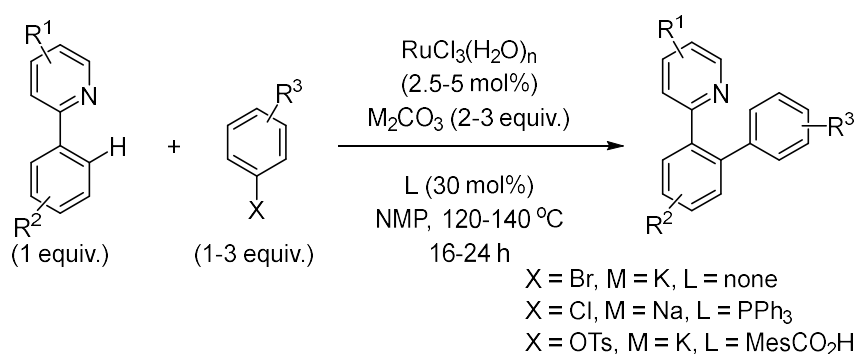


**Scheme 26** Ackermann's postulated reaction mechanism for the ruthenium-catalyzed *ortho*-C-H bond arylation with aryl iodides under visible light irradiation at ambient temperature.

All the above described findings related to bis-cycloruthenated species in *ortho*-C-H bond arylations have been demonstrated for substrates bearing strong  $\text{sp}^2$ -nitrogen-containing directing groups such as pyridine, imidazopyridine, imine, dihydrodibenzoazepin-2-ones, purines, oxazoles, pyrazoles, and triazoles. However, a recent example based on carboxylic directing group has also been reported [124]. In this case, the bis-cycloruthenated species forms thanks to a remote non-covalent ion pair interaction between an ammonium additive and a carboxylate group in the substrate as suggested by computations.

### 3.4. *ortho*-C-H bond arylations with aryl (pseudo)halides employing arene-free ruthenium pre-catalysts.

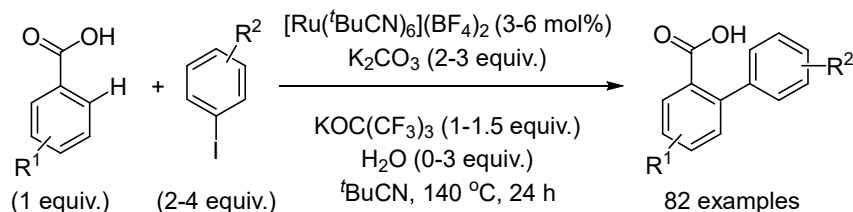
Other powerful ruthenium-based pre-catalysts involve ruthenium complexes that contain no arene ligands coordinated to ruthenium. From the many ruthenium complexes readily available,  $\text{RuCl}_3(\text{H}_2\text{O})_n$  occupies a place of choice, as it is directly extracted from the ores after chemical manipulation and it is the common precursor used for the synthesis of well-defined, mononuclear or dinuclear ruthenium complexes [125].  $\text{RuCl}_3(\text{H}_2\text{O})_n$  is air and moisture stable, features that are interesting for storing purposes. As such, it appears useful and practical for synthetic applications, although its action mode (reaction mechanism) is not fully understood in many cases (*in situ* reduction to Ru(II) species is sound). In this context, Ackermann and co-workers reported the first examples of its successful use as pre-catalyst in *ortho*-C-H bond arylations [126]. This was applied to arylations in NMP with pyridines, oxazolines and pyrazoles as directing groups (Scheme 27). The catalysis was compatible with (hetero)aryl bromides and tosylates, but not that much with aryl chlorides [127]. To circumvent this issue, Yu and co-workers demonstrated that the catalysis was efficient using (hetero)aryl chlorides in the presence of  $\text{PPh}_3$  as ligand in NMP as solvent (Scheme 27) [128] and later Gimeno and co-workers employed the  $\text{RuCl}_3(\text{H}_2\text{O})_n\text{-NaOAc-Zn}$  catalytic system in water [129]. A general methodology was applied to aryl tosylates in the presence of catalytic amounts of  $\text{MesCO}_2\text{H}$  (Scheme 27) [130]. The efficiency of  $\text{RuCl}_3(\text{H}_2\text{O})_n$  pre-catalyst was enhanced in ionic liquids media [103,131] and its recyclability has been achieved by means of heterogeneization as Ru/CeO<sub>2</sub> species [132] and in combination with PEG [133], respectively.



**Scheme 27** *ortho*-C-H bond arylation with aryl (pseudo)halides using  $\text{RuCl}_3(\text{H}_2\text{O})_n$  as the pre-catalyst.

Alternative *para*-cymene-free ruthenium pre-catalysts include the ruthenium(II) complex  $[\text{RuH}(\text{cod})_2]\text{BF}_4$  [134] and the ruthenium(IV) alkylidene complex  $[\text{Cl}_2(\text{PCy}_3)_2\text{Ru}=\text{CHPh}]$  for

reactions similar to those presented in Scheme 27 [135], the  $[\text{RuCl}_2(\text{PPh}_3)_3]$  complex with triazoles as directing groups [136], and the  $[\text{Ru}(\text{tBuCN})_6](\text{BF}_4)_2$  complex with carboxylic acids as directing groups and aryl iodides as arylating agents (Scheme 28) [137].



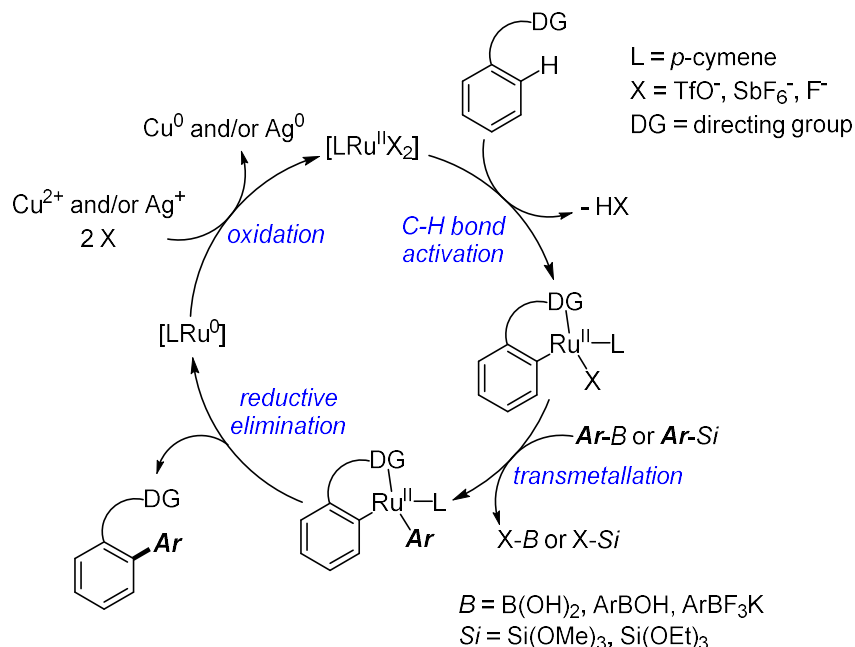
**Scheme 28** *ortho*-C-H bond arylation of benzoic acids with aryl iodides using  $[\text{Ru}(\text{tBuCN})_6](\text{BF}_4)_2$  as the pre-catalyst.

It is worthy to mention that ruthenium-catalyzed *ortho*-C-H bond arylations with aryl (pseudo)halides have successfully been coupled with other ruthenium-catalyzed transformations such as *meta*-C-H bond alkylations [138], oxidations [139] and hydrogenations [119b,140], respectively, *via* one-pot procedures, which is appealing from a sustainable point of view.

#### 4. C-H bond activation followed by oxidation *via* Ru(II/0) catalysis enabling *ortho*-arylation.

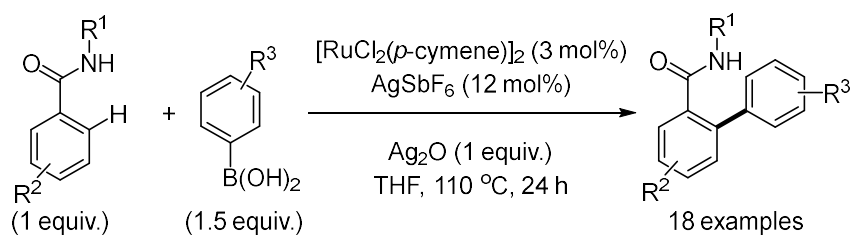
A way to achieve ruthenium-catalyzed *ortho*-C-H bond arylations is by using arylboronic acids  $[\text{ArB}(\text{OH})_2]$  as arylating partners exploiting  $[\text{RuCl}_2(p\text{-cymene})]_2$  as catalyst precursor in the presence of chemical oxidants [69]. The mechanism for such transformation appears in Scheme 29 and it is assisted by ruthenium-coordination to a directing group installed in the aromatic group to be functionalized in the substrate. As in many postulated catalytic cycles relevant for ruthenium-catalyzed *ortho*-C-H bond arylations [69], the initial catalyst formation implies a chloride-free *p*-cymene-ligated ruthenium species. This is achieved *in situ* by means of silver salts and the use of weakly coordinating anions such as triflate ( $\text{TfO}^-$ ), fluoride ( $\text{F}^-$ ) and/or hexafluoroantimonate ( $\text{SbF}_6^-$ ). Ruthenium coordination to the directing group in the substrate further enables C-H bond activation at the *ortho* position with release of acid (i.e.  $\text{TfOH}$ ). The corresponding cyclometallated intermediate was feasible as a five- or six-membered ruthenacycle depending on the nature of the directing group. Subsequent transmetalation at ruthenium(II) with the arylboronic acid partner and further reductive elimination leads to formation of the *ortho*-C-H bond arylated product and ruthenium(0) species. Finally, the active

ruthenium(II) species are regenerated by oxidation with copper(II) and/or silver(I) salts. It is of relevance to note that a similar catalytic cycle may apply when using potassium aryltrifluoroborate ( $\text{ArBF}_3\text{K}$ ) species, diaryl borinic acids ( $\text{Ar}_2\text{BOH}$ ) or arylsilanes [ $\text{ArSi}(\text{OR})_3$ ] as arylating agents instead of  $\text{ArB}(\text{OH})_2$  [141].



**Scheme 29** Mechanism of the *ortho*-C-H bond arylation with aryl boronic acids via Ru(II/0) manifold.

The above-described reaction design has been well applied for substrates bearing so-called weak directing groups such as amides, ketones or thioamides. For instance, Jeganmohan and co-workers reported the ruthenium-catalyzed *ortho*-C-H bond arylation of *N*-alkylbenzamides with aryl boronic acids (Scheme 30) [142]. The group of Szostak showed that the same type of reactivity was observed for *N,N*-dialkylbenzamides with very similar reaction conditions (Scheme 31) [143]. Analogously, the groups of Jeganmohan and Ackermann, independently, demonstrated the ability of acetanilides as suitable substrates for this type of transformation (Scheme 32) [144,145]. In addition, the Ackermann group also showed that diarylborinic acids and potassium aryltrifluoroborates behaved similarly to arylboronic acids. All these methodologies proved tolerant to a wide range of functional groups (alkyl, aryl, ether, ester, alcohol, halide, nitrile, nitro, aldehyde, ketone, thiophene, furan) at different positions of both the substrate and the arylating agent. However, the reactions were not compatible with benzamide (primary amide) as the substrate. Sulfoximines ( $-\text{SONHMe}$ ) as directing groups were equally efficient as secondary amides [146].

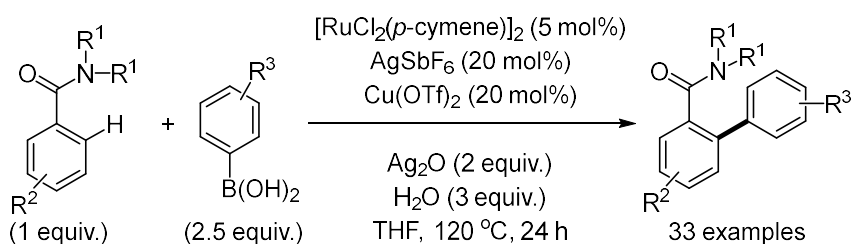


$R^1$  = Me, Et,  $t$ Bu.

$R^2$  = H, 4-Me, 4-I, 4-Br, 4- $\text{NO}_2$ , 4-CN, 4-OMe, 2-naphthyl, 3,4- $\text{OCH}_2\text{O}$ -, 2-thiophenyl.

$R^3$  = H, 4-Br, 4-F, 4-COMe, 4-OMe, 4-OH, 1-naphthyl, 3-thiophenyl.

**Scheme 30** Ruthenium-catalyzed *ortho*-C-H bond arylation of *N*-alkyl benzamides with aryl boronic acids.

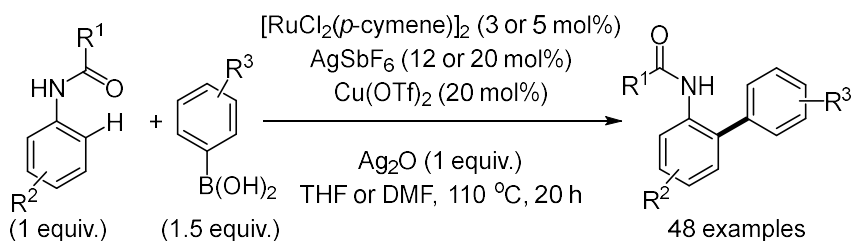


$R^1$  = Me, Et,  $i$ Pr, pyrrolidinyl, piperidinyl, morpholinyl.

$R^2$  = H, 4-Me, 4-OMe, 3,4,5-(OMe) $_3$ , 4-Ph, 4- $\text{NO}_2$ , 4- $\text{CF}_3$ , 4-CHO, 4-COMe, 4- $\text{CO}_2\text{Me}$ , 4-F, 4-Cl, 4-Br, 2-naphthyl, 2-thiophenyl, 2-furanyl.

$R^3$  = H, 4-Me, 4- $t$ Bu, 4-OMe, 4- $\text{CF}_3$ , 4-F, 2,4-(F) $_2$ , 3,5-(F) $_2$ , 4-Cl, 4-Br, 1-naphthyl, 3-thiophenyl.

**Scheme 31** Ruthenium-catalyzed *ortho*-C-H bond arylation of *N,N*-dialkylbenzamides with aryl boronic acids.



$R^1$  = Me, Et,  $i$ Pr,  $t$ Bu.

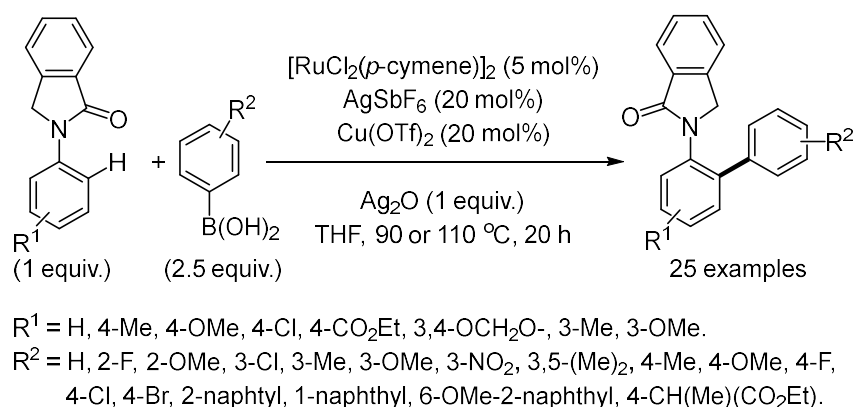
$R^2$  = H, 3-OMe, 4-OMe, 2-Me, 3-Me, 4-Me, 4-Et, 4-Ph, 4-Br, 4-Cl, 4-F, 4-CN, 4- $\text{NO}_2$ , 4- $\text{CO}_2\text{Me}$ , 3-Br, 2-naphthyl, 2-thiophenyl, 4-OH.

$R^3$  = H, 3,4,5-(F) $_3$ , 3,4-(Cl) $_2$ , 4-Me, 4-OMe, 4-COMe, 4-CHO, 3,4- $\text{OCH}_2\text{O}$ -, 2-naphthyl, 4-Cl, 4-Br, 4-I, 3-Br, 3,4-(OMe) $_2$ .

**Scheme 32** Ruthenium-catalyzed *ortho*-C-H bond arylation of acetanilides with aryl boronic acids.

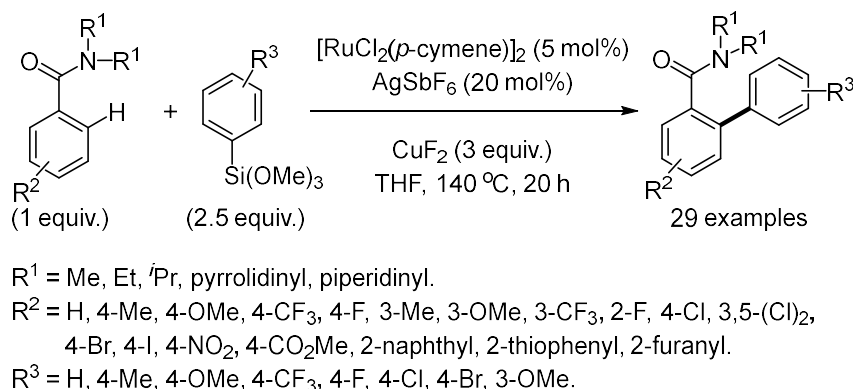


Boronic acids were found to react with *N*-arylisindolinones (cyclic tertiary amides) under ruthenium catalysis to afford selective *ortho*-C-H bond arylation in the anilide ring (Scheme 33) [147]. This constitutes an example of the control of the site-selectivity of the catalysis as two aromatic rings are likely to undergo arylation *a priori* [148]. In this case, a six-membered ruthenacycle is favored over a five-membered one. The methodology was applied in the late-stage functionalization of indoprofen, a blockbuster drug displaying anti-inflammatory properties.



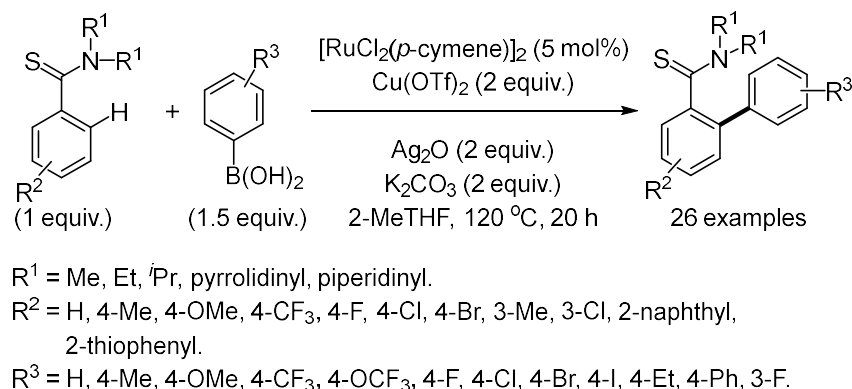
**Scheme 33** Ruthenium-catalyzed *ortho*-C-H bond arylation of tertiary amides with aryl boronic acids.

Acyclic tertiary amides such as *N,N*-dialkylbenzamides underwent ruthenium-catalyzed regioselective *ortho*-C-H bond arylation only upon using an arylsilane such as  $\text{ArSi(OMe)}_3$  [149]. The key for the success of this transformation was the use of over-stoichiometric amounts of  $\text{CuF}_2$  as activator and re-oxidant (Scheme 34). As in the previous example, even when using an excess of aryl coupling partner, selective monofunctionalization was observed. The same reaction conditions were applied to substrates with nitrogen-containing directing groups (i.e. pyridine, pyrazole, quinoline) affording the corresponding *ortho*-C-H bond arylated products [150]. In this case, an excess of arylsilane led to the formation of bis-arylated products.



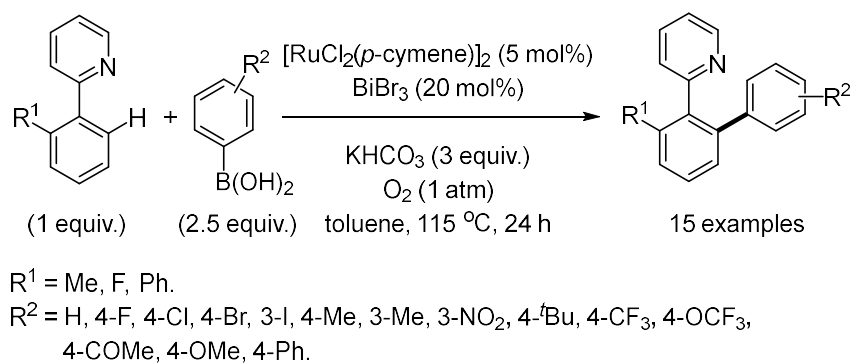
**Scheme 34** Ruthenium-catalyzed *ortho*-C-H bond arylation of tertiary amides with aryl silanes.

Szostak and co-workers reported the ruthenium-catalyzed *ortho*-C-H bond arylation of *N,N*-dialkyl thiobenzamides with boronic acids (Scheme 35) [151]. Control experiments revealed the role of sulfur for ruthenium-coordination as a key step in the catalysis. Interestingly, the reaction was performed using 2-MeTHF as eco-friendly and sustainable solvent. The presence of over-stoichiometric amounts of K<sub>2</sub>CO<sub>3</sub> was critical for an efficient catalytic system, although the exact role of this reagent is not clear.



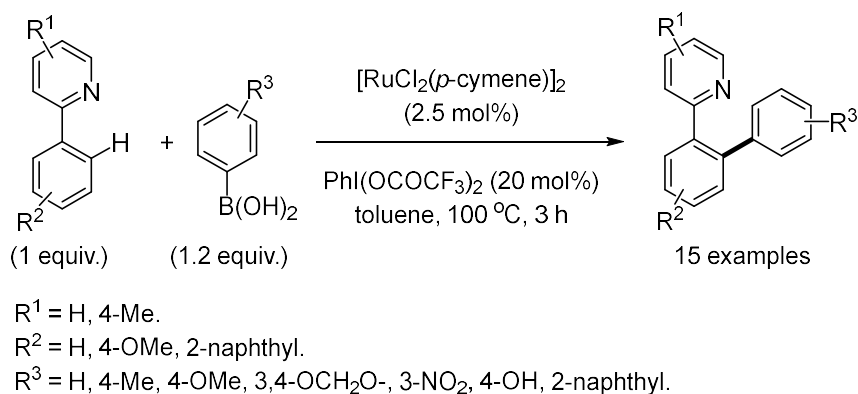
**Scheme 35** Ruthenium-catalyzed *ortho*-C-H bond arylation of thiobenzamides with aryl boronic acids.

Strong nitrogen-containing directing groups have been also studied in this type of transformation. In 2011, Wan and co-workers reported the first examples [87]. By means of ruthenium catalysis, 2'-*o*-substituted 2-phenylpyridine derivatives as substrates afforded the corresponding *ortho*-C-H bond arylated products upon reaction with aryl boronic acids (Scheme 36). Similar observations were made for 1-*o*-tolyl-1*H*-pyrazole substrates (8 examples), in which the pyrazole behaves as equally efficient directing group as pyridine. The combination of BiBr<sub>3</sub> and O<sub>2</sub> appeared to be the chemical oxidant to regenerate the active ruthenium(II) species. Importantly, a kinetic isotope effect  $k_{\text{H}}/k_{\text{D}} = 1.5$  was observed, which strongly suggests that C-H bond cleavage is involved in the rate-limiting step as later shown also by Ackermann and co-workers for acetanilides (*vide supra*) [145].



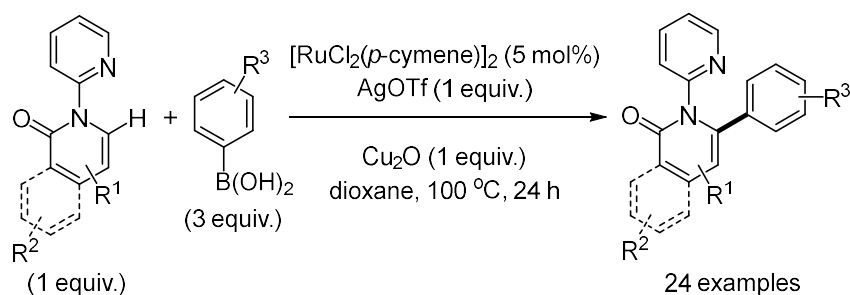
**Scheme 36** Ruthenium-catalyzed *ortho*-C-H bond arylation of 2'-*o*-substituted 2-phenylpyridine derivatives with aryl boronic acids.

Maheswaran and co-workers reported the same type of reactivity for 2-phenylpyridine derivatives using also [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub> as the precatalyst but using iodosobenzene bis(trifluoroacetate) as an organic chemical oxidant (Scheme 37) [152]. The reaction was applied successfully to 1-phenyl-1*H*-pyrazole as well as 9-(pyridin-2-yl)-9*H*-carbazole derivatives.



**Scheme 37** Ruthenium-catalyzed *ortho*-C-H bond arylation of 2-phenylpyridine derivatives with aryl boronic acids.

Substrates appended with pyridine or pyrimidine strong directing groups such as *N*-pyridyl-2-pyridones, *N*-pyridyl-1-isoquinolinones or 9-(pyrimidin-2-yl)-9*H*-carbazole were found suitable substrates towards ruthenium-catalyzed *ortho*-C-H bond arylation using copper(II) or silver(I) salts as chemical oxidants, respectively (Scheme 38 and Scheme 39) [153,154]. These chemical motifs are found as central cores in many biologically relevant molecules, so these methodologies might be of interest for late-stage functionalization and drug discovery.

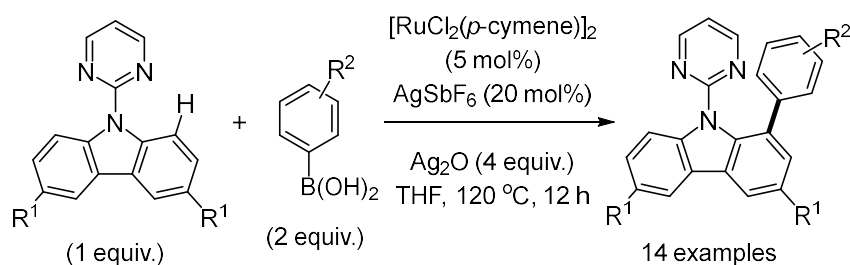


$\text{R}^1 = \text{H}, 4\text{-Me}, 3\text{-Ph}, 5\text{-Cl}, 5\text{-Br}.$

$\text{R}^2 = \text{H}, 6\text{-Cl}, 6\text{-Br}, 6\text{-Ph}, 6,7\text{-(Ph)}_2, 3,4\text{-OCH}_2\text{O-}.$

$\text{R}^3 = \text{H}, 4\text{-OMe}, 4\text{-Me}, 4\text{-F}, 3\text{-CF}_3, 4\text{-Cl}, 3,4\text{-(Cl)}_2, 4\text{-Br}, 3\text{-NO}_2, 4\text{-cyclopentyl}, 2,5\text{-(OMe)}_2, 3,4\text{-(OMe)}_2, 3,4\text{-OCH}_2\text{O-}, 2\text{-naphthyl}, 3\text{-thiophenyl}.$

**Scheme 38** Ruthenium-catalyzed *ortho*-C-H bond arylation of *N*-pyridyl-2-pyridone and *N*-pyridyl-1-isoquinolinones derivatives with aryl boronic acids.

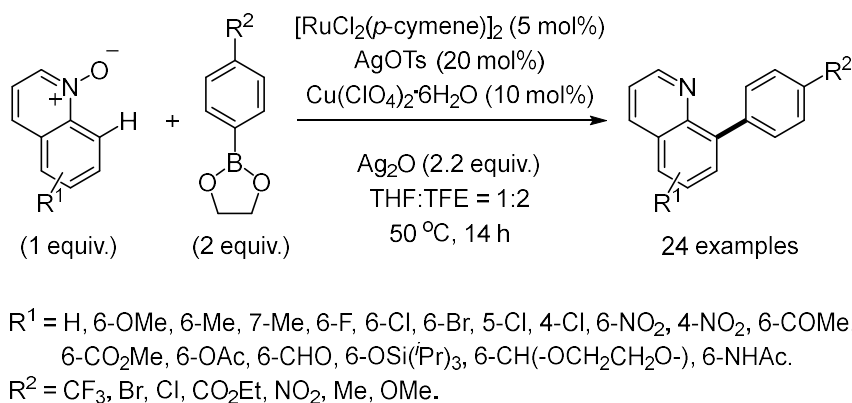


$\text{R}^1 = \text{H}, t\text{Bu}.$

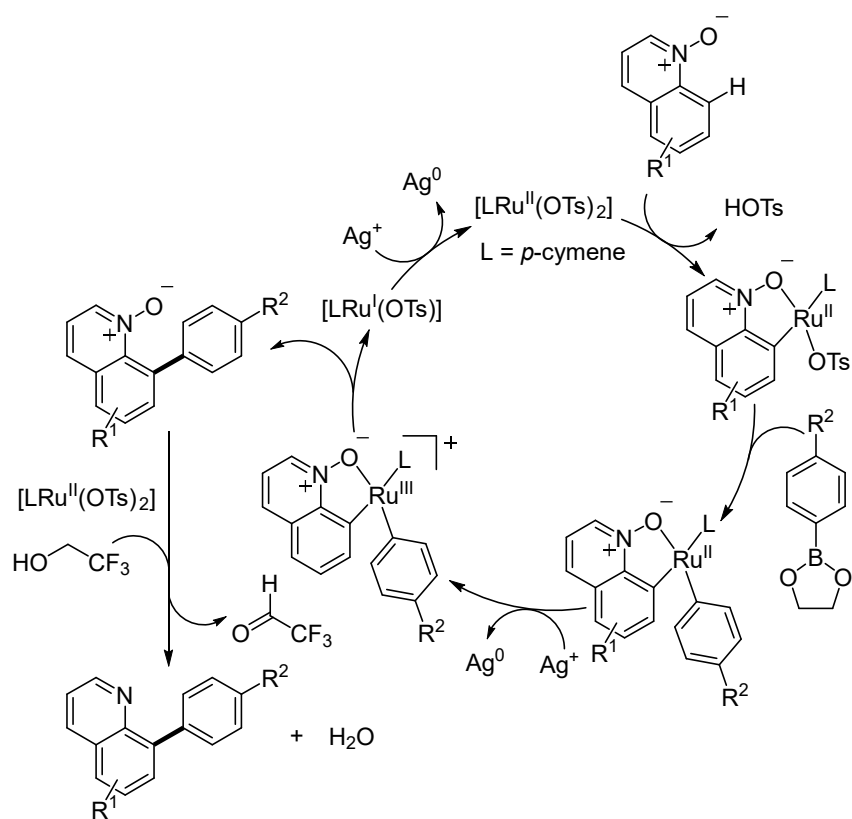
$\text{R}^2 = \text{H}, 4\text{-Me}, 4\text{-CF}_3, 3\text{-CF}_3, 4\text{-OMe}, 3,4\text{-(OMe)}_2, 4\text{-F}, 4\text{-Cl}, 4\text{-I}, 4\text{-CHO}, 1\text{-naphthyl}, 2\text{-dibenzo}[b,d]\text{thiophenyl}.$

**Scheme 39** Ruthenium-catalyzed *ortho*-C-H bond arylation of 9-(pyrimidin-2-yl)-9H-carbazole derivatives with aryl boronic acids.

The group of Chang showed that ruthenium-catalyzed *ortho*-C-H bond arylations using aryl glycol boronic esters are possible using quinoline *N*-oxide derivatives as substrates (Scheme 40) [155]. Besides a broad substrate scope -including polycyclic quinoline derivatives-, in depth mechanistic studies demonstrated that the oxygen atom linked to the nitrogen atom of the quinoline core coordinated to ruthenium prior to the C-H bond activation step. Transmetalation with aryl boronic esters and oxidation afforded a ruthenium(III) species that underwent oxidatively induced reductive elimination (ORE) to afford selective *ortho*-C-H bond arylation [156]. Then, the remaining ruthenium(I) species was oxidized toward the active ruthenium(II) species, whereas a second ruthenium(II) species catalyzed the deoxygenation towards the final product with trifluoroethanol solvent behaving as a reducing agent (Scheme 41).

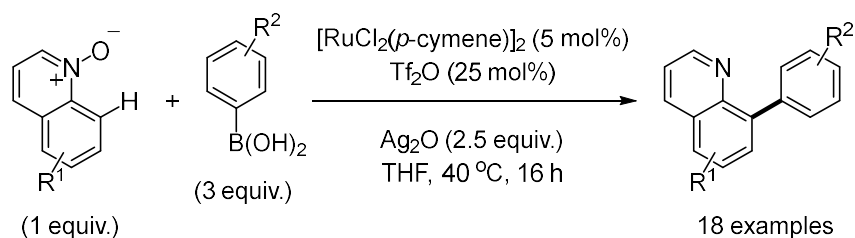


**Scheme 40** Chang's ruthenium-catalyzed *ortho*-C-H bond arylation of quinoline *N*-oxide derivatives with aryl glycol boronic esters.



**Scheme 41** Proposed reaction mechanism for the ruthenium-catalyzed *ortho*-C-H bond arylation of quinoline *N*-oxide derivatives with aryl glycol boronic esters.

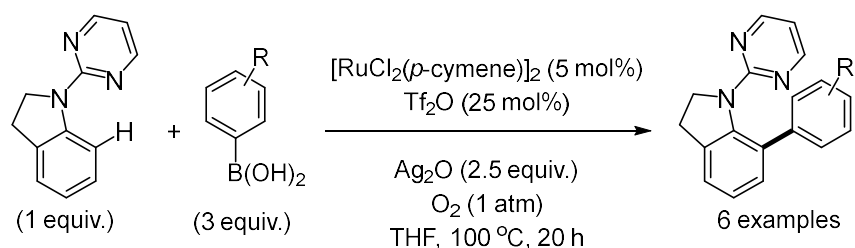
The group of Sharma reported a ruthenium-catalyzed methodology aiming at *ortho*-C-H bond arylation of quinoline *N*-oxides derivatives and *N*-pyrimidin-2-yl-indolines using aryl boronic acids as coupling partners (Scheme 42 and 43) [157]. This time,  $\text{TF}_2\text{O}$  was employed as additive and the methodology was also successfully applied to benzo[*h*]quinoline as well as to 6-(5*H*)-phenanthridinone.



$\text{R}^1 = \text{H}, 2\text{-Me}, 7\text{-Cl}, 2\text{-Ph}, 3\text{-CO}_2\text{Me}, 4\text{-Me}, 6\text{-Me}, 6\text{-OMe}, 6\text{-Br}, 6\text{-NO}_2.$

$\text{R}^2 = \text{H}, 3,5\text{-(Me)}_2, 4\text{-Me}, 4\text{-}^n\text{Pent}, 4\text{-Ph}, 4\text{-OMe}, 4\text{-Cl}, 4\text{-Br}, 4\text{-CHO}.$

**Scheme 42** Sharma's ruthenium-catalyzed *ortho*-C-H bond arylation of quinoline *N*-oxide derivatives with aryl boronic acids.



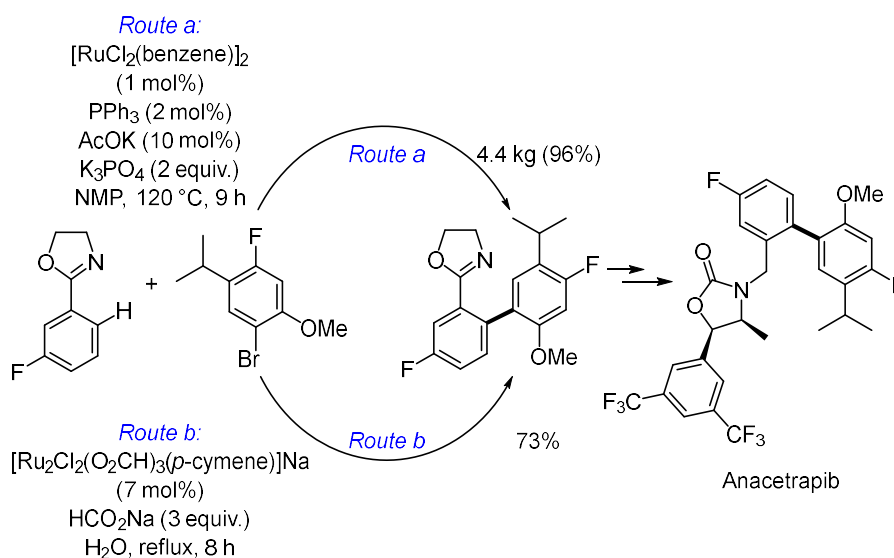
$\text{R} = \text{H}, 4\text{-Cl}, 4\text{-}^n\text{Pent}, 4\text{-CN}, 3,5\text{-(Me)}_2, 3,5\text{-(CF}_3\text{)}_2.$

**Scheme 43** Ruthenium-catalyzed *ortho*-C-H bond arylation of *N*-pyrimidin-2-yl-indoline derivatives with aryl boronic acids.

## 5. Selected, industrially-relevant applications of ruthenium-catalyzed *ortho*-C-H bond arylations.

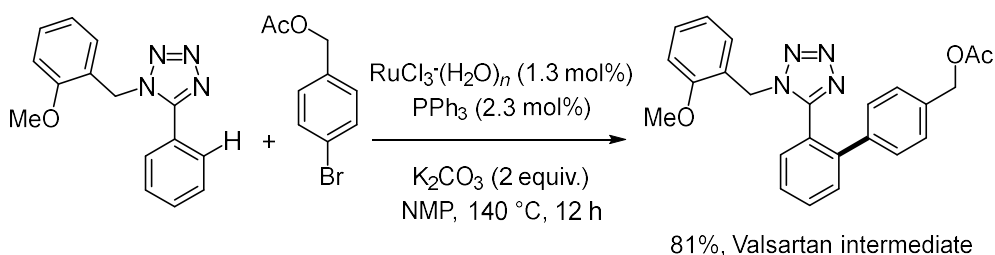
The utilization of direct C-H bond functionalization avoiding synthetic steps for preparation of reactive substrates as well as purification steps presents advantages for industry in terms of green chemistry and sustainability [158]. This is why industry has been rapidly interested in application of direct C-H bond functionalizations. At the Merck company, the synthesis of Anacetrapib, a potent and selective inhibitor of cholesteryl ester transfer protein, has been envisioned at a preparative scale by reaction of a functional bromoaryl substrate with 2-(3-fluorophenyl)oxazoline [159]. This procedure took profit of the oxazoline moiety, which served first as directing group for the *ortho*-C-H bond arylation and was then used for the final steps of the synthesis. The catalytic system based on the  $[\text{RuCl}_2(\text{benzene})]_2$  dimer associated with triphenylphosphine as ligand, potassium acetate as source of acetate ligands and potassium phosphate as a base operated in NMP at 120 °C and gave 96% yield of the arylated oxazoline at a 4 kg scale (Scheme 44 – route a) [159]. Later on, with the objective of proposing a more sustainable procedure avoiding the use of a phosphine additive and the toxic, flammable and

costly NMP solvent, the water-tolerant, ionic ruthenium catalyst  $[\text{Ru}_2\text{Cl}_2(\text{HCOO})_3(p\text{-cymene})]\text{Na}$  was used in water with sodium formate as basic additive to perform the same *ortho*-C-H bond arylation reaction in water under reflux [160]. With this greener catalytic system developed by Chicago Discovery Solutions LLC, starting from equimolar amounts of the two substrates, a conversion of 85% was obtained after 8 hours and the product was isolated in 73% yield (Scheme 44 – route b).

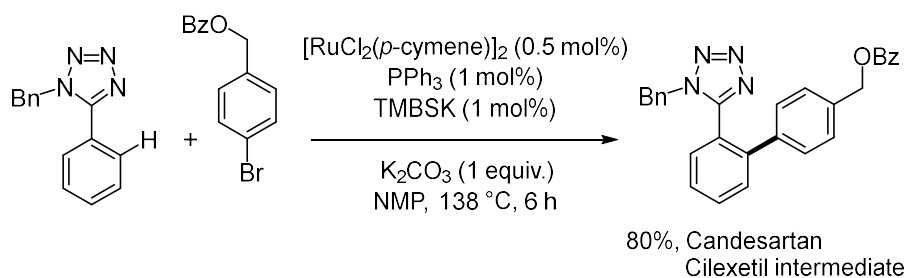


**Scheme 44** Ruthenium-catalyzed *ortho*-C-H bond arylation as the key step in the synthesis of Anacetrapib.

Angiotensin II receptor blockers (ARBs) such as Losartan, Valsartan, Candesartan, Cilxetil, and Olmesartan contain a biphenyltetrazole framework as the key structural motif. At API Corporation (Japan), their synthesis has been considerably improved by constructing the biphenyl substructure by direct C-H bond activation/arylation of a phenyl group equipped with a tetrazole directing group that remains in the final target product. Thus, with  $\text{RuCl}_3 \cdot (\text{H}_2\text{O})_n$  as ruthenium source and triphenylphosphine as ligand, the *ortho*-C-H bond arylation of 1-*N*-protected 2-phenyltetrazole by the appropriate aryl bromide provided selectively the mono-arylated product, precursor of ARBs, in 81% yield when the reaction was carried out in NMP at  $140\text{ }^\circ\text{C}$  for 12 h (Scheme 45) [161]. The binuclear  $[\text{RuCl}_2(p\text{-cymene})]_2$  catalyst precursor was also used in association with  $\text{PPh}_3$  and  $\text{K}_2\text{CO}_3$  as a base in NMP in which the efficiency was improved in the presence of a sterically demanding potassium salt derived from the bis(2-ethylhexyl) phosphate (BEHPK) or the 2,4,6-trimethylbenzenesulfonate (TMBSK) (Scheme 46) [162].



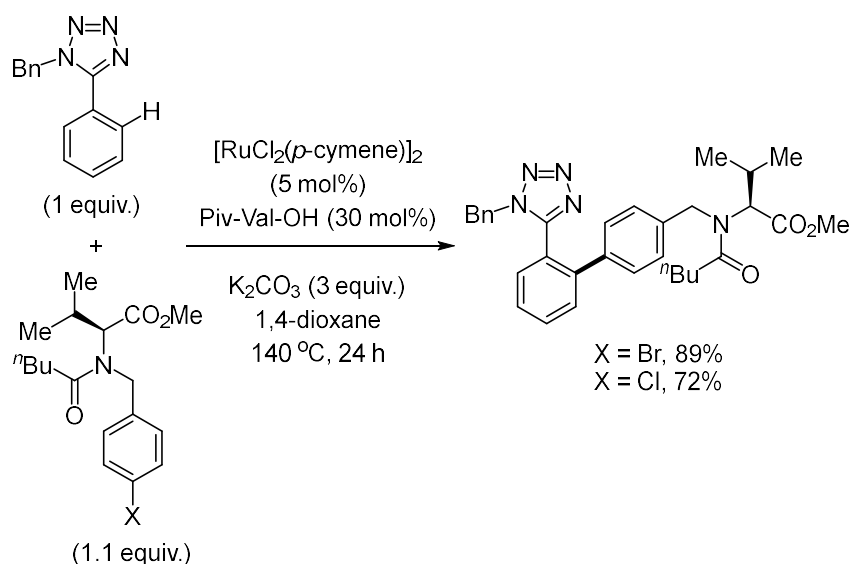
**Scheme 45** Ruthenium-catalyzed *ortho*-C-H bond arylation directed by tetrazole for the preparation of Valsartan.



**Scheme 46** Ruthenium-catalyzed *ortho*-C-H bond arylation directed by tetrazole for the preparation of Valsartan.

The Ackermann group, based on their previous findings related to *ortho*-C-H bond arylation using tetrazoles as directing groups [74d], developed a reaction methodology to access the *N*-protected version of the industrially relevant Valsartan [75c,163]. The reaction of 1-*N*-benzyl 2-phenyltetrazole with a 4-bromo-aryl amino-acid enabled selective *ortho*-C-H bond arylation thanks to a Piv-Val-OH-based ruthenium(II) catalyst (Scheme 47). Importantly, the reaction was also efficient using the less reactive, although more affordable, 4-chloro-aryl amino-acid coupling partner (Scheme 47). From a mechanistic point of view, it was suggested that the carboxylate site from the amino-acid ligand Piv-Val-OH participated in the C-H bond activation step prior to the cycloruthenation. It is relevant to note that ruthenium-catalyzed *ortho*-C-H bond arylations have been implemented in a continuous-flow system [164], although its applicability is scarce.





**Scheme 46** Ruthenium-catalyzed *ortho*-C-H bond arylation of 1-*N*-benzyl 2-phenyltetrazole for accessing *N*-benzyl Valsartan.

## 6. Conclusions.

It is now well accepted that *ortho*-directed aromatic C-H bond arylations proceed *via* an intermediate (five- or six-membered) ruthenacycle arising from coordination of a directing group followed by C-H bond activation and metal-carbon bond formation. This rational, which is based on decades of experimental and computational studies, has enabled a large set of given reaction conditions that enables to use many type of arylating agents as it is described in this chapter. The manifold mechanisms highlighted here demonstrates the compatibility of ruthenium-catalyzed *ortho*-C-H bond arylations with many functional groups, which resulted in important applications for active pharmaceutical ingredients as well as laying the foundation for late-stage arylation. Currently, for the ruthenium(II)-catalyzed methodologies strong nitrogen-containing directing groups have been mostly studied. As such, the exploration of weak directing groups (i.e. ketones, aldehydes, esters, amines) that are prominent in organic synthesis, as well as controlling the site- or positional-selectivity in cases where multiple arylations can occur, remain as two of the major challenges in ruthenium-catalyzed *ortho*-C-H bond arylation chemistry.

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